PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* 20276

Box No. I **TITLE OF INVENTION**

Synergistic Gold-Containing Compositions

Box No. II **APPLICANT**

Name and address: *(Family name followed by given name: for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

Medical Innovations Limited
Unit 2, 83-85 Whiting Street
Artarmon, NSW 2064
Australia

☐ This person is also inventor.

Telephone No.
((612) 9436 0800

Facsimile No.
(612) 9439 2673

Teleprinter No.

State *(i.e. country)* of nationality:
AU

State *(i.e. country)* of residence:
AU

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III **FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)**

Name and address: *(Family name followed by given name: for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

THOMAS, Richard Edward
14 Parnell Street
Killara, NSW 2071
Australia

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(if this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality:
AU

State *(i.e. country)* of residence:
AU

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV **AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE**

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name: for a legal entity, full official designation. The address must include postal code and name of country.)*

SHELSTON WATERS
60 MARGARET STREET
SYDNEY NSW 2000
AUSTRALIA

Telephone No.
(612) 9777 1111

Facsimile No.
(612) 9241 4666

Teleprinter No:

☐ Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No V **DESIGNATION OF STATES**

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

☒ **AP ARIPO Patent:** **KE** Kenya, **LS** Lesotho, **MW** Malawi, **SD** Sudan, **SZ** Swaziland, **UG** Uganda, and any other State which is a Contracting State of the Harare Protocol and of the PCT. **GH** Ghana, **ZW** Zimbabwe

☒ **EA Eurasian Patent:** **AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakstan, **MD** Republic of Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT.

☒ **EP European Patent:** **AT** Austria, **BE** Belgium, **CH and LI** Switzerland and Liechtenstein, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT.

☒ **OA OAPI Patent:** **BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired specify on the line)*

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

☒ **AL** Albania
☒ **AM** Armenia
☒ **AT** Austria
☒ **AU** Australia
☒ **AZ** Azerbaijan
☒ **BA** Bosnia and Herzegovina
☒ **BB** Barbados
☒ **BG** Bulgaria
☒ **BR** Brazil
☒ **BY** Belarus
☒ **CA** Canada
☒ **CH and LI** Switzerland & Liechtenstein
☒ **CN** China
☒ **CU** Cuba
☒ **CZ** Czech Republic
☒ **DE** Germany
☒ **DK** Denmark
☒ **EE** Estonia
☒ **ES** Spain
☒ **FI** Finland
☒ **GB** United Kingdom
☒ **GE** Georgia
☒ **HU** Hungary
☒ **IL** Israel
☒ **IS** Iceland
☒ **JP** Japan
☒ **KE** Kenya
☒ **KG** Kyrgyzstan
☒ **KP** Democratic People's Republic of Korea
☒ **KR** Republic of Korea
☒ **KZ** Kazakstan
☒ **LC** Saint Lucia
☒ **LK** Sri Lanka
☒ **LR** Liberia
☒ **LS** Lesotho
☒ **LT** Lithuania
☒ **LU** Luxembourg
☒ **LV** Latvia
☒ **MD** Republic of Moldova
☒ **MG** Madagascar
☒ **MK** The former Yugoslav Republic of Macedonia
☒ **MN** Mongolia
☒ **MW** Malawi
☒ **MX** Mexico
☒ **NO** Norway
☒ **NZ** New Zealand
☒ **PL** Poland
☒ **PT** Portugal
☒ **RO** Romania
☒ **RU** Russian Federation
☒ **SD** Sudan
☒ **SE** Sweden
☒ **SG** Singapore
☒ **SI** Slovenia
☒ **SK** Slovakia
☒ **TJ** Tajikistan
☒ **TM** Turkmenistan
☒ **TR** Turkey
☒ **TT** Trinidad & Tobago
☒ **UA** Ukraine
☒ **UG** Uganda
☒ **US** United States of America
☒ **UZ** Uzbekistan
☒ **VN** Viet Nam

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

☒ **GH** Ghana
☒ **YU** Yugoslavia
☒ **ZW** Zimbabwe
☒ **SL** Sierra Leone
☒ **ID** Indonesia
☒ **We wish to designate all possible States**

In addition to the designations made above, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except the designation(s) of

The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

Box No. VI **PRIORITY CLAIM** Further priority claims indicated in the Supplemental Box ☐

The priority of the following earlier application(s) is hereby claimed:

Country *(in which, or for which, the application was filed)*	Filing Date *(day/month/year)*	Application No.	Office of filing *(only for regional or international application)*
item (1) AU	4.November 1996 ((04.11.96)	PO3473	
item (2)			

Mark the following check-box if the certified copy of the earlier application is to be issued by the Office which for the purposes of the present international application is the receiving Office (a fee may be required):

☒ The receiving Office is hereby requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s): (1)

Box No. VII **INTERNATIONAL SEARCHING AUTHORITY**

Choice of International Searching Authority (ISA) *(If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):* ISA/___

Earlier Search *Fill in where a search (international, international-type or other) by the International Searching Authority has already been carried out or requested and the Authority is now requested to base the international search, to the extent possible, on the results of that earlier search. Identify such search or request either by reference to the relevant application (or the translation thereof) or by reference to the search request:*

Country (or regional Office): Date *(day/month/year)*: Number:

Box No. VIII **CHECK LIST**

This international application contains the following number of sheets:

1. request	:	3	sheets
2. description	:	24	sheets
3. claims	:	3	sheets
4. abstract	:	1	sheets
5. drawings	:	2	sheets
Total	:	33	sheets

This international application is accompanied by the item(s) marked below:

1. ☐	separate signed power of attorney	5. ☒	fee calculation sheet
2. ☐	copy of general power of attorney	6. ☐	separate indications concerning deposited microorganisms
3. ☐	statement explaining lack of signature	7. ☐	nucleotide and/or amino acid sequence listing (diskette)
4. ☐	priority document(s) *identified in Box No. VI as item(s)*:	8. ☐	other *(specify)*:

Figure No. 1 of the drawings (if any) should accompany the abstract when it is published.

Box No. IX **SIGNATURE OF APPLICANT OR AGENT**

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Paul G Harrison
SHELSTON WATERS

For receiving Office use only

1. Date of actual receipt of the purported international application:
2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority specified by the applicant: ISA/
6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:

SHELSTON WATERS
Level 21
60 Margaret Street
SYDNEY NSW 2000

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

	Date of mailing *day/month/year* 13 JAN 1998
Applicant's or agent's file reference 20276	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. **PCT/AU 97/00747**	International filing date 4 November 1997

Applicant

(1) Medical Innovations Limited
(2) THOMAS, Richard Edward

1. [X] The applicant is hereby notified that the international search report has been established and is transmitted herewith

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau.

If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later)

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the ISA/AU	Authorized officer
AUSTRALIAN INDUSTRIAL PROPERTY ORGANISATION PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No.: (02) 6285 3929	**R.L. POOLEY** Telephone No. (02) 6283 2242

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule" and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasised that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, eg. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Preliminary Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

(i) the claim is unchanged:
(ii) the claim is cancelled;
(iii) the claim is new;
(iv) the claim replaces one or more claims as filed;
(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under Article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequences if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 20276	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/AU 97/00747	International filing date *(day/month/year)* 4 November 1997	(Earliest) Priority Date *(day month/year)* 4 November 1996

Applicant

(1) Medical Innovations Limited

(2) THOMAS, Richard Edward

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of **4** sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [ ] **Certain claims were found unsearchable** (See Box I)

2. [ ] **Unity of invention is lacking** (See Box II)

3. [ ] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing

   [ ] filed with the international application

   [ ] furnished by the applicant separately from the international application,

      [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed

   [ ] transcribed by this Authority

4. With regard to the **title**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

   [X] the text is approved as submitted by the applicant

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:

   Figure No.

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure

   [ ] because this figure better characterises the invention

   [X] None of the figures

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/AU 97/00747

A. CLASSIFICATION OF SUBJECT MATTER

Int Cl[6]: A61K 31/70, 31/28, 31/57, 31/58

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K 31/57, 31/58 and Keywords as below.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
AU: IPC as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Derwent: (Gold or auranofin or aurothiomalate or myocrisin or aurothioglucose or solganol) and (Glucocorticoid: or glucocorticosteroid: or corticosteroid: or mineralocorticoid: or betamethasone or fluocinolone or mometasone or hydrocortisone or fluocortolone or triamcinolone or alclometasone or halcinonide or dexamethasone)
Chemical Abstracts, Medline: As with Derwent above and (psoriasis or synerg: or demat: or immun: or rheumatoid arthritis)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	AU 34351/89 (616755) B (SMITHKLINE BEECHAM CORPORATION) 16 October 1989 Whole Document	1-35

[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 December 1997	13 JAN 1998
Name and mailing address of the ISA/AU AUSTRALIAN INDUSTRIAL PROPERTY ORGANISATION PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No (02) 6285 3929	Authorized officer R.L. POOLEY Telephone No (02) 6283 2242

International Application No.
PCT/AU 97/00747

C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	The Journal of Rheumatology, Volume 21, No. 3, issued March 1994 (Toronto, Canada), M. Heytman et al, "The Longterm Effect of Pulsed Corticosteroids on the Efficacy and Toxicity of Chrysotherapy in Rheumatoid Arthritis", pages 435-441 see especially page 438.	1-8, 11, 13, 15, 20-35
X	Journal of the American Veterinary Medical Association, Volume 186, No.1, Jan 1, 1995, U.S, Ihrke, P et al, "Pemphigus foloaceus in dogs: A review of 37 cases", pages 59-66 see especially page 65, 2nd column.	1-8, 13, 15, 20-35
X	Journal of the American Academy of Dermatology, Volume 16, No. 4, April 1987 US, Thomas .I et al, "Gold Therapy and its indications in dermatology", pages 845-854 see especially page 852.	1-8, 13, 15, 20-35
X	AU, 15456/88 (604542), B (ARTHROPHARM PTY. LIMITED) 10 October 1988 Whole Document	1-8, 10, 11, 13, 15, 17, 18, 20-35

INTERNATIONAL SEARCH REPORT
Information on patent family members

International Application No.
PCT/AU 97/00747

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
AU	34351/89	CA	1337928	DK	2270/90	EP	417105
		JP	7-025681	US	5527779	WO	89-09054
AU	15456/88	CA	1327354	DE	3854604	EP	356435
		JP	2-511829	US	5145841	WO	88-07060

END OF ANNEX

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF RECEIPT OF RECORD COPY

(PCT Rule 24.2(a))

To:

SHELSTON WATERS
60 Margaret Street
Sydney, NSW 2000
AUSTRALIE

RECEIVED 2 [illegible] 1997 SHELSTON WATERS

Date of mailing (day/month/year)	IMPORTANT NOTIFICATION
17 November 1997 (17.11.97)	
Applicant's or agent's file reference	**International application No.**
20276	PCT/AU97/00747

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

MEDICAL INNOVATIONS LIMITED (for all designated States except US)
THOMAS, Richard, Edward (for US)

International filing date	:	04 November 1997 (04.11.97)
Priority date(s) claimed	:	04 November 1996 (04.11.96)
Date of receipt of the record copy by the International Bureau	:	17 November 1997 (17.11.97)
List of designated Offices	:	

AP :GH,KE,LS,MW,SD,SZ,UG,ZW
EA :AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
EP :AT,BE,CH,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE
OA :BF,BJ,CF,CG,CI,CM,GA,GN,ML,MR,NE,SN,TD,TG
National :AL,AM,AT,AU,AZ,BA,BB,BG,BR,BY,CA,CH,CN,CU,CZ,DE,DK,EE,ES,FI,GB,GE,GH,HU, ID,IL,IS,JP,KE,KG,KP,KR,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NO,NZ,PL,PT,RO, RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,UA,UG,US,UZ,VN,YU,ZW

ATTENTION

The applicant should carefully check the data appearing in this Notification. In case of any discrepancy between these data and the indications in the international application, the applicant should immediately inform the International Bureau.

In addition, the applicant's attention is drawn to the information contained in the Annex, relating to:

- [X] time limits for entry into the national phase;
- [ ] confirmation of precautionary designations;
- [ ] requirements regarding priority documents.

A copy of this Notification is being sent to the receiving Office and to the International Searching Authority.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer:

P.Regis

Telephone No. (41-22) 338.83.38

INFORMATION ON TIME LIMITS FOR ENTERING THE NATIONAL PHASE

The applicant is reminded that the "national phase" must be entered before each of the designated Offices indicated in the Notification of Receipt of Record Copy (Form PCT/IB/301) by paying national fees and furnishing translations, as prescribed by the applicable national laws.

The time limit for performing these procedural acts is **20 MONTHS** from the priority date or, for those designated States which the applica[illegible]ects in a demand for international preliminary examination or in a later election, **30 MONTHS** from the priority date, pro[illegible]d that the election is made before the expiration of 19 months from the priority date. Some designated (or elected) Offices have fixed time limits which expire even later than 20 or 30 months from the priority date. In other Offices an extension of time or grace period, in some cases upon payment of an additional fee, is available.

In addition to these procedural acts, the applicant may also have to comply with other special requirements applicable in certain Offices. **It is the applicant's responsibility** to ensure that the necessary steps to enter the national phase are taken in a timely fashion. Most designated Offices do not issue reminders to applicants in connection with the entry into the national phase.

For detailed information about the procedural acts to be performed to enter the national phase before each designated Office, the applicable time limits and possible extensions of time or grace periods, and any other requirements, see the relevant Chapters of Volume II of the PCT Applicant's Guide. Information about the requirements for filing a demand for international preliminary examination is set out in Chapter IX of Volume I of the PCT Applicant's Guide.

GR and ES became bound by PCT Chapter II on 7 September 1996 and 6 September 1997, respectively, and may, therefore, be elected in a demand or a later election filed on or after 7 September 1996 and 6 September 1997, respectively, regardless of the filing date of the international application. (See second paragraph above.)

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

CONFIRMATION OF PRECAUTIONARY DESIGNATIONS

This notification lists only specific designations made under Rule 4.9(a) in the request. It is important to check that these designations are correct. Errors in designations can be corrected where precautionary designations have been made under Rule 4.9(b). The applicant is hereby reminded that any precautionary designations may be confirmed according to Rule 4.9(c) before the expiration of 15 months from the priority date. If it is not confirmed, it will automatically be regarded as withdrawn by the applicant. There will be no reminder and no invitation. Confirmation of a designation consists of the filing of a notice specifying the designated State concerned (with an indication of the kind of protection or treatment desired) and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.

REQUIREMENTS REGARDING PRIORITY DOCUMENTS

For applicants who have not yet complied with the requirements regarding priority documents the following is recalled.

Where the priority of an earlier national (i.e., national or regional) application is claimed, the applic[illegible]must submit a copy of the said national application, certified by the authority with which it was filed ("the priority document") to the receiving Office (which will transmit it to the International Bureau) or directly to the International Bureau, before the expiration of 16 months from the priority date (Rule 17.1).

Where the priority document is issued by the receiving Office, the apolicant may, instead of submitting the priority document, request the receiving Office to prepare and transmit the priority document to the International Bureau. Such request must be made before the expiration of the 16-month time limit.

It is recalled that, where several priorities are claimed, the priority date to be considered for the purposes of computing the 16-month time limit is the filing date of the earliest application whose priority is claimed.

If the priority document concerned is not submitted to the International Bureau before the expiration of the 16-month time limit, or if the request to the receiving Office to transmit the priority document has not been made (and the corresponding fee, if any, paid) before the expiration of this time limit, any designated State may disregard the priority claim.

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OF PRIORITY DOCUMENTS

(PCT Administrative Instructions, Section 411)

To:

SHELSTON WATERS
60 Margaret Street
Sydney, NSW 2000
AUSTRALIE

Date of mailing (day/month/year)
02 December 1997 (02.12.97)

Applicant's or agent's file reference
20276

IMPORTANT NOTIFICATION

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/AU97/00747	04 November 1997 (04.11.97)	04 November 1996 (04.11.96)

Applicant
MEDICAL INNOVATIONS LIMITED et al

The applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to the following application(s):

Priority application No:	Priority date:	Priority country:	Date of receipt of priority document:
PO3473	04 Nov 1996 (04.11.96)	AU	25 Nov 1997 (25.11.97)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer
S. Mafla

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

To:

BALDWIN SHELSTON WATERS
60 Margaret Street
Sydney, NSW 2000
AUSTRALIE

RECEIVED
SYDNEY
3 - JUL 1998
BALDWIN SHELSTON WATERS

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

Date of mailing (day/month/year)
22 June 1998 (22.06.98)

Applicant's or agent's file reference
20276

IMPORTANT NOTIFICATION

International application No.
PCT/AU97/00747

International filing date (day/month/year)
04 November 1997 (04.11.97)

1. The following indications appeared on record concerning:

[ ] the applicant [ ] the inventor [X] the agent [ ] the common representative

Name and Address
SHELSTON WATERS
60 Margaret Street
Sydney, NSW 2000
Australia

State of Nationality:
State of Residence:
Telephone No.: (612) 9777 1111
Facsimile No.: (612) 9241 4666
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address
BALDWIN SHELSTON WATERS
60 Margaret Street
Sydney, NSW 2000
Australia

State of Nationality:
State of Residence:
Telephone No.: (612) 9777 1111
Facsimile No.: (612) 9241 4666
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer
P. Regis

Telephone No.: (41-22) 338.83.38

Form PCT IB/306 (March 1994)

002095435

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

To:

SHELSTON WATERS
60 Margaret Street
Sydney, NSW 2000
AUSTRALIE

RECEIVED
29 MAY 1998
BALDWIN SHELSTON WATERS

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

Date of mailing (day/month/year) 14 May 1998 (14.05.98)		
Applicant's or agent's file reference 20276 — file with CWT.	**IMPORTANT NOTICE**	
International application No. PCT/AU97/00747	**International filing date** (day/month/year) 04 November 1997 (04.11.97)	**Priority date** (day/month/year) 04 November 1996 (04.11.96)
Applicant MEDICAL INNOVATIONS LIMITED et al		

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,BR,CA,CN,EP,IL,JP,KP,KR,NO,PL,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AL,AM,AP,AT,AZ,BA,BB,BG,BY,CH,CU,CZ,DE,DK,EA,EE,ES,FI,GB,GE,GH,HU,ID,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NZ,OA,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,UA,UG,UZ,VN,YU,ZW
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on 14 May 1998 (14.05.98) under No. WO 98/19683

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland** Facsimile No. (41-22) 740.14.35	Authorized officer J. Zahra Telephone No. (41-22) 338.83.38

File copy

PCT/AU97/00747

PATENT COOPERATION TREATY

17

From the INTERNATIONAL BUREAU

PCT

INFORMATION CONCERNING ELECTED OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

To:

BALWIN SHELSTON WATERS
60 Margaret Street
Sydney, NSW 2000
AUSTRALIE

Date of mailing (day/month/year)
19 June 1998 (19.06.98)

Applicant's or agent's file reference
20276

IMPORTANT INFORMATION

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/AU97/00747	04 November 1997 (04.11.97)	04 November 1996 (04.11.96)

Applicant
MEDICAL INNOVATIONS LIMITED et al

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

   AP :GH,KE,LS,MW,SD,SZ,UG,ZW
   EP :AT,BE,CH,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE
   National :AU,BG,BR,CA,CN,CZ,DE,GB,IL,JP,KP,KR,MN,NO,NZ,PL,RO,RU,SE,SK,US,
   VN

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

   EA :AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
   OA :BF,BJ,CF,CG,CI,CM,GA,GN,ML,MR,NE,SN,TD,TG
   National :AL,AM,AT,AZ,BA,BB,BY,CH,CU,DK,EE,ES,FI,GE,GH,HU,ID,IS,KE,KG,KZ,
   LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MW,MX,PT,SD,SG,SI,SL,TJ,TM,TR,TT,UA,UG,UZ,
   YU,ZW

3. The applicant is reminded that he must enter the "national phase" before the expiration of 30 months from the priority date before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing , if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 36(3)(b) and Rule 74.1).

   Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

   The entry into the European regional phase is postponed until 31 months from the priority date for all States designated for the purposes of obtaining a European patent.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer:
P. Regis

Telephone No. (41-22) 338.83.38

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The name or two-letter code of that Authority must be indicated by the applicant on the line below:

PEA/ _____

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty.

For International Preliminary Examining Authority use only	
Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION

Applicant's or agent's file reference: 20276

International application No.	International filing date *(day/month/year)*	(Earliest) Priority date *(day/month/year)*
PCT/AU97/00747	4 November 1997 (04.11.97)	4 November 1996 (04.11.96)

Title of invention: Syngergistic Gold-Containing Compositions

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Medical Innovations Limited
Unit 2, 83-85 Whiting Street
Artarmon, NSW 2064
Australia

Telephone No.: (612) 9436 0800
Facsimile No.: (612) 9439 2673
Teleprinter No.:

State *(i.e. country)* of nationality: AU
State *(i.e. country)* of residence: AU

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

THOMAS, Richard Edward
14 Parnell Street
Killara, NSW 2071
Australia

State *(i.e. country)* of nationality: AU
State *(i.e. country)* of residence: AU

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(i.e. country)* of nationality:
State *(i.e. country)* of residence:

☐ Further applicants are indicated on a continuation sheet.

International application No.
PCT/AU97/00747

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is [X] agent [ ] common representative

and [X] has been appointed earlier and represents the applicant(s) also for international preliminary examination.

[ ] is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

[ ] is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Baldwin Shelston Waters (Formerly Shelston Waters)
60 Margaret Street
Sydney, NSW 2000
Australia

Telephone No.: (612) 9777 1111

Facsimile No.: (612) 9241 4666

Teleprinter No.:

[ ] Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV STATEMENT CONCERNING AMENDMENTS

The applicant wishes the International Preliminary Examining Authority*

(i) [X] to start the international preliminary examination on the basis of the international application as originally filed.

(ii) [ ] to take into account the amendments under Article 34 of

- [ ] the description (amendments attached).
- [ ] the claims (amendments attached).
- [ ] the drawings (amendments attached).

(iii) [ ] to take into account any amendments of the claims under Article 19 filed with the International Bureau (a copy is attached).

(iv) [ ] to disregard any amendments of the claims made under Article 19 and to consider them as reversed.

(v) [ ] to postpone the start of the international preliminary examination until the expiration of 20 months from the priority date unless that Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Box No. V ELECTION OF STATES

[X] The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT)* except .....

.....

.....

.....

(If the applicant does not wish to elect certain eligible States, the name(s) or country code(s) of those States must be indicated above.)

International application No.
PCT/AU97/00747

Box No. VI CHECK LIST

The demand is accompanied by the following documents for the purposes of international preliminary examination:

			For International Preliminary Examining Authority use only: received	not received
1. amendments under Article 34				
description	:	sheets	☐	☐
claims	:	sheets	☐	☐
drawings	:	sheets	☐	☐
2. letter accompanying amendments under Article 34	:	sheets	☐	☐
3. copy of amendments under Article 19	:	sheets	☐	☐
4. copy of statement under Article 19	:	sheets	☐	☐
5. other *(specify)*:	:	sheets	☐	☐

The demand is also accompanied by the item(s) marked below:

1. ☐ separate signed power of attorney
2. ☐ copy of general power of attorney
3. ☐ statement explaining lack of signature
4. ☒ fee calculation sheet
5. ☐ other *(specify)*:

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

Paul G Harrison
Baldwin Shelston Waters

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:
2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):
3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. ☐ The applicant has been informed accordingly.
4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.
5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: Agent :

BALDWIN SHELSTON WATERS
Level 21
60 Margaret Street
SYDNEY NSW 2000

RECEIVED
11 JUN 1998
BALDWIN SHELSTON WATERS

PCT

NOTIFICATION OF RECEIPT OF DEMAND

(PCT Rule 61.1(b), first sentence and Administrative Instructions, Section 601)

Applicant's or agent's file reference: 20276	Date of mailing (day/month/year): 10 JUN 1998 (10/6/98)
	IMPORTANT NOTIFICATION

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/AU97/00747	4 NOV 1997 (4/11/97)	4 NOV 1996 (4/11/96)

Applicant: Medical Innovations Limited (et al.)

1. The applicant is hereby notified that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:

   4 JUN 1998 (4/6/98)

2. This date of receipt is:

   [X] the actual date of receipt of the demand.

   [ ] the date on which the proper corrections to the demand were timely received.

3. [ ] This date is **AFTER** the expiration of 19 months from the priority date.

   Attention: The election(s) made in the demand does (do) not have the effect of postponing the commencement of the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)). Therefore, the acts for entry into the national phase must be performed within 20 months from the priority date (or later in some Offices) (Article 22).

   For details, see Annex B to Form PCT/IB/301 sent by the International Bureau and Volume II of the PCT Applicant's Guide.

   [ ] This notification confirms the information given in person or by telephone on:

   _____

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

Name and mailing address of the IPEA/AU	Authorized officer
AUSTRALIAN PATENT OFFICE **PO BOX 200, WODEN ACT 2606,** **AUSTRALIA**	(Mrs) Cecilia TRACEY
Facsimile No. 02 6285 3929	Telephone No. (02) 6283 2511

Form PCT/IPEA/402 (July 1992)

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Baldwin Shelston Waters
Level 21
60 Margaret Street
SYDNEY NSW 2000

RECEIVED
SYDNEY
23 JUN 1998
BALDWIN SHELSTON WATERS

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *day/month/year*	22 JUN 1998
Applicant's or agent's file reference P3510 YS/jls	REPLY DUE within **two months** from the above date of mailing

International application No.	International filing date	Priority Date
PCT/AU 97/00747	4 November 1997	4 November 1996

International Patent Classification (IPC) or both national classification and IPC

Int. Cl.[6] A61K 31/70, 31/28, 31/57, 31/58

Applicant

(1) MEDICAL INNOVATIONS LIMITED
(2) THOMAS, Richard Edward

1. This written opinion is the **first** (first, etc) drawn by this International Preliminary Examining Authority.
2. This opinion contains indications relating to the following items:.

I	[X]	Basis of the opinion
II	[ ]	Priority
III	[ ]	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	[ ]	Lack of unity of invention
V	[X]	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	[ ]	Certain documents cited
VII	[X]	Certain defects in the international application
VIII	[ ]	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4*bis*.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: **4 March 1999**

Name and mailing address of the IPEA/AU	Authorized Officer
AUSTRALIAN PATENT OFFICE PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No. (02) 6285 3929	R.L. POOLEY Telephone No. (02) 6283 2242

Form PCT/IPEA/408 (Cover sheet) (January 1994)copbko

WRITTEN OPINION

International application No.
PCT/AU 97/00747

I. Basis of the opinion

1. This opinion has been drawn on the basis of *(Substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".)*:

[X] the international application as originally filed.

[ ] the description, pages , as originally filed,
pages , filed with the demand,
pages , filed with the letter of .

[ ] the claims, Nos. , as originally filed,
Nos. , as amended under Article 19,
Nos. , filed with the demand,
Nos. , filed with the letter of .

[ ] the drawings, sheets/fig , as originally filed,
sheets/fig , filed with the demand,
sheets/fig , filed with the letter of .

2. The amendments have resulted in the cancellation of:

[ ] the description, pages

[ ] the claims, Nos.

[ ] the drawings, sheets/fig

3. [ ] This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

4. Additional observations, if necessary:

Please note that claims 1-29 are subject matter of rule 67.1 (methods of treatment of humans) and as such do not require an international preliminary examination. However, because the subject matter does not contravene Australian law these claims have been examined.

WRITTEN OPINION

International application No.
PCT/AU 97/00747

V. **Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims Claims 1-35	YES NO
Inventive step (IS)	Claims Claims 1-35	YES NO
Industrial applicability (IA)	Claims 1-35 Claims	YES NO

2. Citations and explanations

NOVELTY (N): Claims 1-35

D1 AU 34351/89 (616755) B

D2 The Journal of Rheumatology, Volume 21, No: 3, pages 435-441, Heytman et al, "The Longterm Effect of Pulsed Corticosteroids on the Efficacy and Toxicity of Chrysotherapy in Rheumatoid Arthritis"

D3 Journal of the American Veterinary Association, Volume 186, No: 1, pages 59-66, Ihrke et al, "Pemphigus foloaceus in dogs: A review of thirty-seven cases"

D4 Journal of the American Academy of Dermatology, Volume 16, No: 4, pages 845-854, Thomas et al, "Gold Therapy and its Indications in Dermatology"

D5 AU 15456/88 (604542) B

The above citations all disclose combination treatment of various immune-mediated disorders with gold compounds and corticosteroids. These combination treatments are stated to be synergistic, adjunctive or to provide side-effect attenuation and could fall within the ambit of "synergistically' as presently claimed. Note that the present claims 1, 7 and 30 require synergy between the gold and corticosteroid components, but do not clearly specify the nature and action of this synergism. The above citations also disclose the treatment of the claimed disorders and administration through the claimed modes of administration. Consequently they disclose all the features of claims 1-11, 13, 15 and 20-35.

Furthermore document D1 specifically discloses synergistic administration of auranolin with betamethasone diproprionate for the treatment of psoriasis. It also discloses the gold compound in lipid soluble form. Consequently this citation further discloses the embodiments of claims 12, 14 and 16-19.

INVENTIVE STEP (IS): Claims 1-35

Claims 1-35: as above.

VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

(i) Claims 1, 7 and 30 are not fully supported by the description. Claims 1 and 30 are directed to the use of all synergistic gold/corticosteroid combinations for the treatment of any manifestation of an immune mediated disorder. However the description has only disclosed a surprising or unexpected effect for the application of specific gold/corticosteroid combinations to specific manifestations (eg betanethasone dipropionate/auranofin for epidermial hyperplasia). Although claim 7 requires the treatment of specific manifestations it still includes the application of any synergistic gold/corticosteroid combination. It is considered that an undue burden of experimentation would be placed on the skilled person to determine all synergistic gold/corticosteroid combinations applicable to all manifestations of immune-mediated disorders, especially as synergy is generally surprising and unexpected by its nature.

(ii) Claims 1 and 7 are unclear because it is not clear that the preferential action is synergistic. This also applies to claim 30 in respect of the differential action, although it is unclear how the differential action differs from preferential action. It is also unclear whether the term synergistically as used in claims 1, 7 and 30 is intended to define the characteristics of page 22 lines 12-17.

[redacted]ENT COOPERATION TRE[redacted]

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Baldwin Shelston Waters
Level 21
60 Margaret Street
SYDNEY NSW 2000

RECEIVED
SYDNEY
26 OCT 1998
BALDWIN SHELSTON WATERS

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	23 OCT 1998
Applicant's or agent's file reference 20276 IAR:ajw.wls	**REPLY DUE** within **ONE MONTH** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority Date *(day/month/year)*
PCT/AU 97/00747	4 November 1997	4 November 1996

International Patent Classification (IPC) or both national classification and IPC

Int. Cl.[6] A61K 31/70, 31/28, 31/57, 31/58

Applicant

(1) MEDICAL INNOVATIONS LIMITED
(2) THOMAS, Richard Edward

1. This written opinion is the **Second** (first, etc) drawn by this International Preliminary Examining Authority.
2. This opinion contains indications relating to the following items:.

I	[X]	Basis of the opinion
II	[ ]	Priority
III	[ ]	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	[ ]	Lack of unity of invention
V	[X]	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	[ ]	Certain documents cited
VII	[ ]	Certain defects in the international application
VIII	[X]	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4*bis*.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: **4 March 1999**

Name and mailing address of the IPEA/AU	Authorized Officer
AUSTRALIAN PATENT OFFICE PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No. (02) 6285 3929	**R.L. POOLEY** Telephone No. (02) 6283 2242

WRITTEN OPINION

International application No.
PCT/AU 97/00747

I. Basis of the opinion

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed.

☒ the description, pages **1, 2, 6-24,** as originally filed,
pages , filed with the demand,
pages **3-5,** filed with the letter of **22 September 1998.**

☒ the claims, pages , as originally filed,
pages , as amended under Article 19,
pages , filed with the demand,
pages **25-28,** filed with the letter of **22 September 1998.**

☒ the drawings, pages **1-2,** as originally filed,
pages , filed with the demand,
pages , filed with the letter of .

☐ the sequence listing part of the description:
pages , as originally filed
pages , filed with the demand
pages , filed with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages

☐ the claims, Nos.

☐ the drawings, sheets/fig

5. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"*

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	**30, 31, 32, 34**	**YES**
	Claims	**1-29, 33, 35, 36, 37**	**NO**
Inventive step (IS)	Claims		**YES**
	Claims	**1-37**	**NO**
Industrial applicability (IA)	Claims	**1-37**	**YES**
	Claims		**NO**

2. Citations and explanations

NOVELTY (N) Claims 1-29, 33, 35-37

D1 AU 34351/89 (616755) B

D2 The Journal of Rheumatology, Volume 21, No.3, pages 435-441, Heytman et al, "The Longterm Effect of Pulsed Corticosteroids on the Efficacy and Toxicity of Chrysotherapy in Rheumatoid Arthritis"

D3 Journal of the American Veterinary Association, Volume 186, No.1, pages 59-66, Ihrke et al, "Pemphigus foloaceus in dogs: A review of thirty-seven cases"

D4 Journal of the American Academy of Dermatology, Volume 16, No.4, pages 845-854, Thomas et al, "Gold Therapy and its Indications in Dermatology"

D5 AU 15456/88 (604542)B

Documents D1-D5 all disclose combination treatment of various immune-mediated disorders with gold compounds and corticosteroids. The treatments of D2-D5 are disclosed to be adjunctive or to provide side-effect attenuation. However the psoriasis treatment of document D1 is stated to be synergistic, and this document discloses the presently preferred synergistic formulation of auranofin acid betamethasone dipropionate.

Claim 29 and its dependent claims 33, 35, 36 and 37 are not distinguished from the disclosures of document D1. Claim 29 includes synergistic formulations of auranofin acid betamethasone dipropionate by virtue of the disclosure of these formulations as preferred embodiments, and there is nothing in claim 29 to distinguish these claimed synergistic formulations from those of the document D1. Claim 29 as presently drafted appears to include mechanisms by which these formulations achieve synergy, but such mechanisms are incapable of conferring novelty on the formulations per se.

Claim 1 as presently drafted can still include the administration of compounds as alternative or adjunctive therapy, and consequently remains anticipated by documents D1-D5. The last line of the claim limits the compounds to exhibit equal action to each component of the disorder, but this action is not necessarily synergistic. Furthermore the synergistic action would be anticipated by document D1 which discloses synergistic treatments by the presently preferred compounds to the same locus (eg a psoriasis patient). The embodiments of the dependent claims of claim 1 are disclosed at various points throughout documents D1-D5 (eg the different modes of administration of the formulations) In addition claim 6 would not seem to be clearly differentiated from the disclosures of document D1, which includes synergistic compositions of a gold compound and one or more corticosteroids (eg betamethasone dipropionate and any other corticosteroid).

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 36 and 37 are incorrectly appended in that they are directed to method claims, but are appended to claims 35 and 29 which are compostion claims.

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Box V

INVENTIVE STEP (IS) Claims 1-37

Claims 1-29, 33, 35-37 : as above

Claims 30, 31, 32, 34:

These claims merely involve the formulation of the composition of claim 29 for administration by various modes, and such formulation would be routine to a skilled person. The different formulation modes do not provide advantages which would be surprising or unexpected over the disclosed mode of topical administration.

INDUSTRIAL APPLICABILLITY (IA) Claims 1-37

Claims 1-37 are industrially applicable.

Please note that claims 1-28 are subject matter of rule 67.1 (methods of treatment of humans) and as such do not require an international preliminary examination. However, because the subject matter does not contravene Australian law these claims have been examined.

TENT COOPERATION TREA

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 20276 IAR : ajw.wls	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
International application No. **PCT/AU 97/00747**	International filing date *(day/month/year)* 4 November 1997	Priority Date *(day/month/year)* 4 November 1996

International Patent Classification (IPC) or national classification and IPC

Int. Cl.[6] A61K 31/70, 31/28, 31/57, 31/58

Applicant

MEDICAL INNOVATIONS LIMITED et al

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of **5** sheets, including this cover sheet.

   [X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of **7** sheet(s).

3. This report contains indications relating to the following items:

I	[X]	Basis of the report
II	[ ]	Priority
III	[ ]	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	[ ]	Lack of unity of invention
V	[X]	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	[ ]	Certain documents cited
VII	[ ]	Certain defects in the international application
VIII	[X]	Certain observations on the international application

Date of submission of the demand 4 June 1998	Date of completion of the report 10 December 1998
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No. (02) 6285 3929	Authorized Officer **R.L. POOLEY** Telephone No. (02) 6283 2242

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/AU 97/00747

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed.

☒ the description, pages **1, 2, 6-24,** as originally filed,
pages , filed with the demand,
pages **3-5,** filed with the letter of **22 September 1998.**

☒ the claims, pages , as originally filed,
pages , as amended (together with any statement) under Article 19,
pages , filed with the demand,
pages **25-28,** filed with the letter of **22 September 1998.**

☒ the drawings, pages **1-2,** as originally filed,
pages , filed with the demand,
pages , filed with the letter of .

☐ the sequence listing part of the description:
pages , as originally filed
pages , filed with the demand
pages , filed with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, was on the basis of the sequence listing:

☐ contained in the international application in written form.

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4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages

☐ the claims, Nos.

☐ the drawings, sheets/fig

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report*

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	**30, 31, 32, 34**	**YES**
	Claims	**1-29, 33, 35, 36, 37**	**NO**
Inventive step (IS)	Claims		**YES**
	Claims	**1-37**	**NO**
Industrial applicability (IA)	Claims	**1-37**	**YES**
	Claims		**NO**

2. Citations and explanations (Rule 70.7)

NOVELTY (N) Claims 1-29, 33, 35-37

D1 AU 34351/89 (616755) B

D2 The Journal of Rheumatology, Volume 21, No.3, pages 435-441, Heytman et al, "The Longterm Effect of Pulsed Corticosteroids on the Efficacy and Toxicity of Chrysotherapy in Rheumatoid Arthritis"

D3 Journal of the American Veterinary Association, Volume 186, No.1, pages 59-66, Ihrke et al, "Pemphigus foloaceus in dogs: A review of thirty-seven cases"

D4 Journal of the American Academy of Dermatology, Volume 16, No.4, pages 845-854, Thomas et al, "Gold Therapy and its Indications in Dermatology"

D5 AU 15456/88 (604542)B

Documents D1-D5 all disclose combination treatment of various immune-mediated disorders with gold compounds and corticosteroids. The treatments of D2-D5 are disclosed to be adjunctive or to provide side-effect attenuation. However the psoriasis treatment of document D1 is stated to be synergistic, and this document discloses the presently preferred synergistic formulation of auranofin and betamethasone dipropionate.

Claim 29 and its dependent claims 33, 35, 36 and 37 are not distinguished from the disclosures of document D1. Claim i29 includes synergistic formulations of auranofin and betamethasone dipropionate by virtue of the disclosure of these formulations as preferred embodiments, and there is nothing in claim 29 to distinguish these claimed synergistic formulations from those of the document D1. Claim 29 as presently drafted appears to include mechanisms by which these formulations achieve synergy, but such mechanisms are incapable of conferring novelty on the formulations per se.

Claim 1 as presently drafted can still include the administration of compounds as alternative or adjunctive therapy, and consequently remains anticipated by documents D1-D5. The last line of the claim limits the compounds to exhibit equal action to each component of the disorder, but this action is not necessarily synergistic. Furthermore the synergistic action would be anticipated by document D1 which discloses synergistic treatments by the presently preferred compounds to the same locus (eg a psoriasis patient). The embodiments of the dependent claims of claim 1

continued

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 36 and 37 are incorrectly appended in that they are directed to method claims, but are appended to claims 35 and 29 which are composition claims.

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of : BOX V

are disclosed at various points throughout documents D1-D5 (eg the different modes of administration of the formulations). In addition claim 6 would not seem to be clearly differentiated from the disclosures of document D1, which includes synergistic compositions of a gold compound and one or more corticosteroids (eg betamethasone dipropionate and any other corticosteroid).

INVENTIVE STEP (IS) Claims 1-37

Claims 1-29, 33, 35-37 : as above

Claims 30, 31, 32, 34:

These claims merely involve the formulation of the composition of claim 29 for administration by various modes, and such formulation would be routine to a skilled person. The different formulation modes do not provide advantages which would be surprising or unexpected over the disclosed mode of topical administration.

INDUSTRIAL APPLICABILITY (IA) Claims 1-37

Claims 1-37 are industrially applicable.

Please note that claims 1-28 are subject matter of rule 67.1 (methods of treatment of humans) and as such do not require an international preliminary examination. However, because the subject matter does not contravene Australian law these claims have been examined.

type of effect potentiated, when combined with a gold compound. That is to say, different corticosteroids, when combined with a gold compound, do not all have the expected similarity of synergistic action against inflammation and also demonstrate differential synergistic action with respect to inflammation and hyperplasia. In the compositions of the present invention certain corticosteroids synergise with the gold compound to provide a greater effect on the inflammatory component of a disorder, such as psoriasis, while other corticosteroids give rise to compositions with preferential effects on cellular hyperproliferation. It is contemplated that the compositions of the present invention could be effectively used also for the treatment of a variety of systemic, tissue-specific or localised immune, autoimmune and inflammatory disorders.

SUMMARY OF THE INVENTION

According to a first aspect the invention consists in a method of treating an immune-mediated disorder having an inflammatory component and/or a cellular hyperproliferation component, comprising the step of administering to a patient requiring such treatment a gold compound and at least one corticosteroid, wherein the at least one corticosteroid is selected to interact with the gold compound to exhibit preferential synergistic action towards one of the components of said disorder or to exhibit equal action towards each component of said disorder.

According to a preferred embodiment the present invention consists in a method of treating an immune mediated disorder according to the first aspect comprising the step of administering at least two corticosteroids, at least one of which is selected to interact with the gold compound to exhibit preferential synergistic action towards the inflammatory component, and at least another is selected to interact with the gold compound to exhibit preferential synergistic action towards the cellular hyperproliferation component of said disorder.

According to another preferred embodiment the present invention consists in a method of treating an immune-mediated disorder having multiple components, comprising the step of administering to a patient requiring such treatment one or more compositions comprising a gold compound and one or more corticosteroids, wherein the corticosteroid is selected to provide a composition with equal synergistic action towards each component of said disorder.

According to another preferred embodiment the present invention consists in a method of treating an immune-mediated disorder having one or more components,

comprising the step of administering to a patient requiring such treatment a composition comprising a gold compound and one or more compositions comprising one or more corticosteroids wherein the corticosteroid is selected to provide a composition with preferential synergistic activity towards one of the components of said disorder and wherein the composition comprising a gold compound is administered orally and the one or more compositions comprising one or more corticosteroids is administered topically, in amounts effective to provide a composition of gold and a corticosteroid having preferential synergistic action towards said component.

Preferably the component of the immune-mediated disorder is an inflammatory component and/or a cellular hyperproliferation component and the composition comprises at least two corticosteroids, one of which is selected to provide a composition with preferential synergistic action towards the inflammatory component and the second corticosteroid is selected to provide a composition with preferential synergistic action towards the cellular hyperproliferation component of said disorder.

Preferably the disorder to be treated is an immune-mediated dermatological disorder which is associated with more than one component. Examples of immune-mediated dermatological disorders include psoriasis or dermatitis such as contact, atopic or seborrheic dermatitis. Other disorders include rheumatoid arthritis. Typical components of such disorders include an inflammatory component and/or a cellular hyperproliferation component. The corticosteroid can be selected to provide a composition with synergistic activity towards cellular hyperproliferation in preference to inflammation or *vice versa*. Such a corticosteroid can be, for example, betamethasone dipropionate, fluocinolone acetonide or hydrocortisone. In cases where inflammation needs to be targeted in preference to cellular hyperproliferation, the corticosteroid can be betamethasone dipropionate, fluocinolone acetonide or mometasone furoate.

The composition is suitably formulated for topical administration.

Where the immune-mediated disorder is characterised by a number of different components, the preferred method of treatment could employ one or more compositions comprising a gold compound and one or more corticosteroids, wherein the corticosteroids are selected to provide composition(s) with preferential activity towards only one of the components of said disorder. Thus the treatment of each individual

component is achieved through use of composition(s) comprising one or more selected corticosteroids, which may be applied in the form of two or more separate compositions or a single composition comprising two or more corticosteroids.

Preferably the gold compounds used in the present invention are lipid soluble. Even more preferably the gold compounds used are formulated for topical application. However, it will be understood that systemically or locally administered compositions are also within the scope of the present invention including those administered by injection, preferably intra-articularly. In this regard the corticosteroid can be formulated for oral, topical, systemic or local administration.

According to second aspect the present invention consists in a pharmaceutical composition comprising a gold compound and one or more corticosteroids, the corticosteroid being selected to interact with the gold compound to exhibit a preferential synergistic action towards an inflammatory component and/or a cellular hyperproliferation component of an immune-mediated disorder, in combination with a pharmaceutically acceptable carrier, excipient, adjuvant or solvent.

Preferably the gold compound is auranofin and the corticosteroid is selected from the group comprising hydrocortisone acetate, hydrocortisone, betamethasone, betamethasone dipropionate, dexamethasone, fluocortolone 21-pivalate, triamcinolone acetonide, betamethasone valerate, alclometasone dipropionate, halcinonide, mometasone furoate or fluocinolone acetonide. More preferably the corticosteroid is selected from the group comprising hydrocortisone, betamethasone dipropionate, mometasone furoate or fluocinolone acetonide.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. A method of treating an immune-mediated disorder having an inflammatory component and/or a cellular hyperproliferation component, comprising the step of administering to a patient requiring such treatment a gold compound and at least one corticosteroid, wherein the at least one corticosteroid is selected to interact with the gold compound to exhibit preferential synergistic action towards one of the components of said disorder or to exhibit equal action towards each component of said disorder.

2 A method of treating an immune-mediated disorder according to claim 1 wherein the disorder has an inflammatory component and a cellular hyperproliferation component.

3. A method of treating an immune-mediated disorder according to any one of the preceding claims wherein the gold compound and the at least one corticosteroid are administered simultaneously.

4. A method of treating an immune-mediated disorder according to any one of the preceding claims wherein the gold compound and the at least one corticosteroid are administered sequentially.

5. A method of treating an immune-mediated disorder according to claim 4 wherein the at least one corticosteroid is administered after the gold compound.

6. A method of treating an immune mediated disorder according to any one of the preceding claims comprising the step of administering at least two corticosteroids, at least one of which is selected to interact with the gold compound to exhibit preferential synergistic action towards the inflammatory component, and at least another is selected to interact with the gold compound to exhibit preferential synergistic action towards the cellular hyperproliferation component of said disorder.

7. A method according to any one of the preceding claims, wherein the disorder is an immune-mediated dermatological disorder.

8. A method according to claim 7, wherein the disorder is psoriasis.

9. A method according to claim 7, wherein the disorder is dermatitis.

10. A method according to any one of claims 1 to 6 wherein the disorder is rheumatoid arthritis.

11. A method according to any one of the preceding claims, wherein the gold compound is lipid soluble.

12. A method according to any one of the preceding claims, wherein the at least one corticosteroid is selected to interact with the gold compound to exhibit synergistic activity towards cellular hyperproliferation in preference to inflammation.

13. A method according to claim 12, wherein the at least one corticosteroid is selected from the group consistin of betamethasone dipropionate, fluocinolone acetonide and hydrocortisone.

14. A method according to any one of the preceding claims, wherein the at least one corticosteroid is selected to interact with the gold compound to exhibit synergistic activity towards inflammation in preference to cellular hyperproliferation.

15. A method according to claim 14, wherein the at least one corticosteroid is selected from the group consisting of betamethasone dipropionate, fluocinolone acetonide and mometasone furoate.

16. A method according to claim 10 wherein the corticosteroid is selected from the group comprising hydrocortisone acetate, hydrocortisone, betamethasone, betamethasone dipropionate, dexamethasone, fluocortolone 21-pivalate, triamcinolone acetonide, betamethasone valerate, alclometasone dipropionate, halcinonide, mometasone furoate and fluocinolone acetonide.

17. A method according to claim 16 wherein the corticosteroid is selected from the group comprising hydrocortisone, betamethasone dipropionate, mometasone furoate and fluocinolone acetonide.

18. A method according to any one of the preceding claims wherein the gold compound is auranofin.

19. A method according to any one the preceding claims, wherein the gold compound is administered systemically.

20. A method according to any one of claims 1 to 18, wherein the gold compound is administered orally.

21. A method according to any one of claims 1 to 18, wherein the gold compound is administered locally.

22. A method according to any one of claims 1 to 18, wherein the gold compound is administered topically.

23. A method according to any one of claims 1 to 18, wherein the gold compound is administered by intra-articular injection.

24. A method according to any one of the preceding claims, wherein the at least one corticosteroid is administered systemically.

25. A method according to any one of claims 1 to 23, wherein the at least one corticosteroid is administered orally.

26. A method according to any one of claims 1 to 23, wherein the at least one corticosteroid is administered locally.

27. A method according to any one of claims 1 to 23, wherein the at least one corticosteroid is administered topically.

28. A method according to any one of claims 1 to 23, wherein the at least one corticosteroid is administered by intra-articular injection.

29. A pharmaceutical composition comprising a gold compound and one or more corticosteroids, the corticosteroid being selected to interact with the gold compound to exhibit a preferential synergistic action towards an inflammatory component and/or a cellular hyperproliferation component of an immune-mediated disorder, in combination with a pharmaceutically acceptable carrier, excipient, adjuvant or solvent.

30. A pharmaceutical composition according to claim 29, wherein the composition is formulated for systemic administration.

31. A pharmaceutical composition according to claim 29, wherein the composition is formulated for oral administration.

32. A pharmaceutical composition according to claim 29, wherein the composition is formulated for local administration.

33. A pharmaceutical composition according to claim 29, wherein the composition is formulated for topical administration.

34. A pharmaceutical composition according to claim 29, wherein the composition is formulated for administration by intra-articular injection.

35. A pharmaceutical composition according to any one of claims 29 to 34, wherein the corticosteroid is selected from the group comprising hydrocortisone acetate, hydrocortisone, betamethasone, betamethasone dipropionate, dexamethasone, fluocortolone 21-pivalate, triamcinolone acetonide, betamethasone valerate, alclometasone dipropionate, halcinonide, mometasone furoate and fluocinolone acetonide.

36. A method according to claim 35 wherein the corticosteroid is selected from the group comprising hydrocortisone, betamethasone dipropionate, mometasone furoate and fluocinolone acetonide.

37. A method according to any one of claims 29 to 36, wherein the gold compound is auranofin.

DATED this 22nd Day of September 1998

MEDICAL INNOVATIONS LIMITED

Attorney: PAUL G. HARRISON
Fellow Institute of Patent Attorneys of Australia
of BALDWIN SHELSTON WATERS

BALDWIN SHELSTON WATERS
SYDNEY NSW 2000

Speed Dial 508

Contact: Dr Ivan Rajkovic

Date: 22 September, 1998

The International Preliminary Examining Authority
Australian Patent Office
PO Box 200
WODEN ACT 2606

URGENT: 22 SEPTEMBER 1998 DEADLINE

Sir

Re: PCT Application No. PCT/AU**97/00747** dated **4th November 1997**
Applicant: **Medical Innovations Limited**
Our Ref: 20276 IAR:ajw.wls

We refer to the First Written Opinion of the International Preliminary Examining Authority mailed on 19th August 1998 in respect of the above application.

Pursuant to Article 34, the Applicant requires the International Preliminary Examining Authority to take into account the amendments on the enclosed replacement pages as set forth on the attached Statement of Amendments.

The following comments are offered as to the differences between the replaced sheet(s) and the replacement sheet(s).

Description

Original pages:

Pages 3 to 5:	amended (to include amended consistory clauses)

Claims

Original claims:

Claims 1 to 4:	amended
Claim 5:	as originally filed
Claim 6:	cancelled
Claim 7:	amended and renumbered (new claim 6)
Claims 8:	renumbered (new claim 7)
Claims 9 to 11	amended and renumbered (new claims 8 to 10)
Claim 12:	renumbered (new claim 11)
Claims 13 to 18:	amended and renumbered (new claims 12 to 17)
Claim 19 to 20:	renumbered (new claims 18 to 19)
Claims 21 to 24:	amended and renumbered (new claims 20 to 23)
Claim 25:	renumbered (new claim 24)
Claims 26 to 35:	amended and renumbered (new claims 25 to 34)
	New claims 35 to 37 added

COMMENTS

Regarding the novelty objection in light of documents D1 to D5, the Examiner's attention is drawn to the fact that citations D2 to D5 do not in fact mention or suggest any form of synergy between gold compounds and corticosteroids. The gold or corticosteriods in the prior art are used as alternative or adjunctive therapy, making use of the full strength of each active agent without the realisation and teaching that synergy can occur and that considerably smaller dosages of each active agent can be used in combination to achieve the same or superior therapeutic effect. Further, none of the citations D1 to D5 suggest that a corticosteroid can be selected for a particular type of action, for example, to selectively or differentially synergise in their action towards a specific manifestation of a disorder, namely either inflammation or cellular hyperproliferation. Such differential selectivity is not described or even suggested in any citation and was not known to occur before the disclosure of the present specification. Even when considering the disclosure of D1, a skilled addressee would not and could not realise or suspect that betamethasone dipropionate was differentially synergistic for a particular manifestation of an immune-mediated disorder, and thus would not be motivated to select this corticosteroid on the basis of such a criterion.

From the disclosure of the present specification it can be clearly seen that, for example, mometasone furoate does not synergise with gold in inhibiting epidermal thickness, however, it does synergise in its action towards inflammation (see Figures 1 and 2). Further the present invention also teaches how to select particular corticosteriods with respect to their relative activities against, for example, cellular hyperproliferation or inflammation. These concepts are not taught or suggested in the citations and a skilled reader would not be motivated to make any selection of a corticosteroid on the basis of the teaching of the prior art, and certainly not on the basis of differential synergy. Therefore we believe that the prior art citations are not in any way relevant to either novelty or inventive step of the presently claimed invention.

As to the inventive step objection, we believe that the proposed amendments to the claims and the above discussion also address this objection. We believe that it would be clear to those skilled in the art that if preferential synergistic action can be achieved towards specific components of an immune disorder, which like inflammation and cellular hyperproliferation represent discrete manifestations applicable to any tissue location, that such a principle can be applied to a number of different immune-mediated disorders where they occur as a component of the disorder.

The present specification also discloses for the first time the relative potencies of different corticosteriods with respect to inflammation and cellular hyperproliferation. Thus, based on the teaching of the present specification a skilled reader would be able to achieve the appropriate combination of a gold compound and a corticosteroid for the treatment of either the inflammatory or cellular hyperproliferation component, or both, of an immune mediated disorder, whatever the nature or tissue location of that disorder.

To expedite the prosecution of the application, we have proposed amendments to the claims, a component of which is the restriction of the claims to immune mediated disorders which have an inflammatory and/or cellular hyperproliferation components. Please note that the examples used to demonstrate the invention are merely convenient models of inflammation and cellular hyperproliferation, since both can be induced by simple means in the same animal model and the collection and analysis of tissue samples using such a model are relatively straightforward. The underlying mechanisms of inflammation and cellular hyperproliferation observed in this model, and the method of action of gold and corticosteroids, is representative of such ev ents in other immune mediated disorders and tissue locations where inflammation and/or cellular hyperproliferation may be a component of the disorder. This would be recognised by those skilled in the art. Further, it would also be clear to those skilled in the art that "cellular proliferation" refers to proliferation of cells of the affected tissue as well as to those of the immune system.

Well known examples of tissue hyperplasia associated with immunologically-induced diseases include:

- Hyperplasia of synoviocytes in the joints of patients with rheumatoid arthritis. This gives rise to the hypertrophied structure known as a pannus that causes erosion of the underlying cartilage.

- Hyperplasia of the epidermis in psoriasis and seborrhoeic dermatitis (the latter includes dandruff)
-
- Hyperplasia of thyroid tissue in Graves' disease.
- Fibrosis and hyperplasia of the ductal lining of certain exocrine glands in Sjögren's syndrome.
- Various types of hypertrophy associates with different features of systemic lupus erythematosus, e.g. proliferation of endothelial cells in SLE-associated glomerulonephritis.

These and other similar examples are all well known and accepted in this field of technology.

Thus there would be no difficulty in extrapolating from the models of inflammation/cellular hyperproliferation and gold/corticosteroid combinations provided by the present invention to the use of such combinations in treatment of any immune mediate disorder having inflammation and/or cellular hyperproliferation as a component.

Regarding the term "synergistically" or "synergistic", the definition given on page 22, lines 12 to 17, merely states what would already be clear to those skilled in the art in relation to the meaning of this term. Thus the meaning of the term as used in the claims would not be unclear to those skilled in the art.

We trust the proposed amendments and the above discussion fully address the outstanding objections and therefore respectfully request that a clear report be established.

Yours respectfully
BALDWIN SHELSTON WATERS

Encl.

BALDWIN SHELSTON WATERS
SYDNEY NSW 2000

Speed Dial 508

Contact: Ivan A Rajkovic

Date: 22 September, 1998

The International Preliminary Examining Authority
Australian Patent Office
PO Box 200
WODEN ACT 2606

Re: PCT Application No. PCT/AU97/00747 dated 4 November 1997
Applicant: MEDICAL INNOVATIONS LIMITED
Our Ref: 20276/IAR.jp.wls

STATEMENT OF PROPOSED AMENDMENTS

Complete Specification

Description

1. Cancel pages 3 to 5 now on file and replace with new pages 3 to 5 filed herewith in duplicate.

Claims

2.. Cancel pages 25 to 27 now on file and replace with new pages 25 to 28 filed herewith in duplicate.

DATED this 22nd Day of September, 1998.

MEDICAL INNOVATIONS LIMITED

by
Fellow Institute of Patent Attorneys of Australia
of BALDWIN SHELSTON WATERS

type of effect potentiated, when combined with a gold compound. That is to say, different corticosteroids, when combined with a gold compound, do not all have the expected similarity of synergistic action against inflammation and also demonstrate differential synergistic action with respect to inflammation and hyperplasia. In the compositions of the present invention certain corticosteroids synergise with the gold compound to provide a greater effect on the inflammatory component of a disorder, such as psoriasis, while other corticosteroids give rise to compositions with preferential effects on cellular hyperproliferation. It is contemplated that the compositions of the present invention could be effectively used also for the treatment of a variety of systemic, tissue-specific or localised immune, autoimmune and inflammatory disorders.

SUMMARY OF THE INVENTION

According to a first aspect the invention consists in a method of treating an immune-mediated disorder having an inflammatory component and/or a cellular hyperproliferation component, comprising the step of administering to a patient requiring such treatment a gold compound and at least one corticosteroid, wherein the at least one corticosteroid is selected to interact with the gold compound to exhibit preferential synergistic action towards one of the components of said disorder or to exhibit equal action towards each component of said disorder.

According to a preferred embodiment the present invention consists in a method of treating an immune mediated disorder according to the first aspect comprising the step of administering at least two corticosteroids, at least one of which is selected to interact with the gold compound to exhibit preferential synergistic action towards the inflammatory component, and at least another is selected to interact with the gold compound to exhibit preferential synergistic action towards the cellular hyperproliferation component of said disorder.

According to another preferred embodiment the present invention consists in a method of treating an immune-mediated disorder having multiple components, comprising the step of administering to a patient requiring such treatment one or more compositions comprising a gold compound and one or more corticosteroids, wherein the corticosteroid is selected to provide a composition with equal synergistic action towards each component of said disorder.

According to another preferred embodiment the present invention consists in a method of treating an immune-mediated disorder having one or more components,

comprising the step of administering to a patient requiring such treatment a composition comprising a gold compound and one or more compositions comprising one or more corticosteroids wherein the corticosteroid is selected to provide a composition with preferential synergistic activity towards one of the components of said disorder and wherein the composition comprising a gold compound is administered orally and the one or more compositions comprising one or more corticosteroids is administered topically, in amounts effective to provide a composition of gold and a corticosteroid having preferential synergistic action towards said component.

Preferably the component of the immune-mediated disorder is an inflammatory component and/or a cellular hyperproliferation component and the composition comprises at least two corticosteroids, one of which is selected to provide a composition with preferential synergistic action towards the inflammatory component and the second corticosteroid is selected to provide a composition with preferential synergistic action towards the cellular hyperproliferation component of said disorder.

Preferably the disorder to be treated is an immune-mediated dermatological disorder which is associated with more than one component. Examples of immune-mediated dermatological disorders include psoriasis or dermatitis such as contact, atopic or seborrheic dermatitis. Other disorders include rheumatoid arthritis. Typical components of such disorders include an inflammatory component and/or a cellular hyperproliferation component. The corticosteroid can be selected to provide a composition with synergistic activity towards cellular hyperproliferation in preference to inflammation or *vice versa*. Such a corticosteroid can be, for example, betamethasone dipropionate, fluocinolone acetonide or hydrocortisone. In cases where inflammation needs to be targeted in preference to cellular hyperproliferation, the corticosteroid can be betamethasone dipropionate, fluocinolone acetonide or mometasone furoate.

The composition is suitably formulated for topical administration.

Where the immune-mediated disorder is characterised by a number of different components, the preferred method of treatment could employ one or more compositions comprising a gold compound and one or more corticosteroids, wherein the corticosteroids are selected to provide composition(s) with preferential activity towards only one of the components of said disorder. Thus the treatment of each individual

component is achieved through use of composition(s) comprising one or more selected corticosteroids, which may be applied in the form of two or more separate compositions or a single composition comprising two or more corticosteroids.

Preferably the gold compounds used in the present invention are lipid soluble. Even more preferably the gold compounds used are formulated for topical application. However, it will be understood that systemically or locally administered compositions are also within the scope of the present invention including those administered by injection, preferably intra-articularly. In this regard the corticosteroid can be formulated for oral, topical, systemic or local administration.

According to second aspect the present invention consists in a pharmaceutical composition comprising a gold compound and one or more corticosteroids, the corticosteroid being selected to interact with the gold compound to exhibit a preferential synergistic action towards an inflammatory component and/or a cellular hyperproliferation component of an immune-mediated disorder, in combination with a pharmaceutically acceptable carrier, excipient, adjuvant or solvent.

Preferably the gold compound is auranofin and the corticosteroid is selected from the group comprising hydrocortisone acetate, hydrocortisone, betamethasone, betamethasone dipropionate, dexamethasone, fluocortolone 21-pivalate, triamcinolone acetonide, betamethasone valerate, alclometasone dipropionate, halcinonide, mometasone furoate or fluocinolone acetonide. More preferably the corticosteroid is selected from the group comprising hydrocortisone, betamethasone dipropionate, mometasone furoate or fluocinolone acetonide.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. A method of treating an immune-mediated disorder having an inflammatory component and/or a cellular hyperproliferation component, comprising the step of administering to a patient requiring such treatment a gold compound and at least one corticosteroid, wherein the at least one corticosteroid is selected to interact with the gold compound to exhibit preferential synergistic action towards one of the components of said disorder or to exhibit equal action towards each component of said disorder.

2 A method of treating an immune-mediated disorder according to claim 1 wherein the disorder has an inflammatory component and a cellular hyperproliferation component.

3. A method of treating an immune-mediated disorder according to any one of the preceding claims wherein the gold compound and the at least one corticosteroid are administered simultaneously.

4. A method of treating an immune-mediated disorder according to any one of the preceding claims wherein the gold compound and the at least one corticosteroid are administered sequentially.

5. A method of treating an immune-mediated disorder according to claim 4 wherein the at least one corticosteroid is administered after the gold compound.

6. A method of treating an immune mediated disorder according to any one of the preceding claims comprising the step of administering at least two corticosteroids, at least one of which is selected to interact with the gold compound to exhibit preferential synergistic action towards the inflammatory component, and at least another is selected to interact with the gold compound to exhibit preferential synergistic action towards the cellular hyperproliferation component of said disorder.

7. A method according to any one of the preceding claims, wherein the disorder is an immune-mediated dermatological disorder.

8. A method according to claim 7, wherein the disorder is psoriasis.

9. A method according to claim 7, wherein the disorder is dermatitis.

10. A method according to any one of claims 1 to 6 wherein the disorder is rheumatoid arthritis.

11. A method according to any one of the preceding claims, wherein the gold compound is lipid soluble.

12. A method according to any one of the preceding claims, wherein the at least one corticosteroid is selected to interact with the gold compound to exhibit synergistic activity towards cellular hyperproliferation in preference to inflammation.

13. A method according to claim 12, wherein the at least one corticosteroid is selected from the group consistin of betamethasone dipropionate, fluocinolone acetonide and hydrocortisone.

14. A method according to any one of the preceding claims, wherein the at least one corticosteroid is selected to interact with the gold compound to exhibit synergistic activity towards inflammation in preference to cellular hyperproliferation.

15. A method according to claim 14, wherein the at least one corticosteroid is selected from the group consisting of betamethasone dipropionate, fluocinolone acetonide and mometasone furoate.

16. A method according to claim 10 wherein the corticosteroid is selected from the group comprising hydrocortisone acetate, hydrocortisone, betamethasone, betamethasone dipropionate, dexamethasone, fluocortolone 21-pivalate, triamcinolone acetonide, betamethasone valerate, alclometasone dipropionate, halcinonide, mometasone furoate and fluocinolone acetonide.

17. A method according to claim 16 wherein the corticosteroid is selected from the group comprising hydrocortisone, betamethasone dipropionate, mometasone furoate and fluocinolone acetonide.

18. A method according to any one of the preceding claims wherein the gold compound is auranofin.

19. A method according to any one the preceding claims. wherein the gold compound is administered systemically.

20. A method according to any one of claims 1 to 18, wherein the gold compound is administered orally.

21. A method according to any one of claims 1 to 18, wherein the gold compound is administered locally.

22. A method according to any one of claims 1 to 18, wherein the gold compound is administered topically.

23. A method according to any one of claims 1 to 18, wherein the gold compound is administered by intra-articular injection.

24. A method according to any one of the preceding claims, wherein the at least one corticosteroid is administered systemically.

25. A method according to any one of claims 1 to 23, wherein the at least one corticosteroid is administered orally.

26. A method according to any one of claims 1 to 23, wherein the at least one corticosteroid is administered locally.

27. A method according to any one of claims 1 to 23, wherein the at least one corticosteroid is administered topically.

28. A method according to any one of claims 1 to 23, wherein the at least one corticosteroid is administered by intra-articular injection.

29. A pharmaceutical composition comprising a gold compound and one or more corticosteroids, the corticosteroid being selected to interact with the gold compound to exhibit a preferential synergistic action towards an inflammatory component and/or a cellular hyperproliferation component of an immune-mediated disorder, in combination with a pharmaceutically acceptable carrier, excipient, adjuvant or solvent.

30. A pharmaceutical composition according to claim 29, wherein the composition is formulated for systemic administration.

31. A pharmaceutical composition according to claim 29, wherein the composition is formulated for oral administration.

32. A pharmaceutical composition according to claim 29, wherein the composition is formulated for local administration.

33. A pharmaceutical composition according to claim 29, wherein the composition is formulated for topical administration.

34. A pharmaceutical composition according to claim 29, wherein the composition is formulated for administration by intra-articular injection.

35. A pharmaceutical composition according to any one of claims 29 to 34, wherein the corticosteroid is selected from the group comprising hydrocortisone acetate, hydrocortisone, betamethasone, betamethasone dipropionate, dexamethasone, fluocortolone 21-pivalate, triamcinolone acetonide, betamethasone valerate, alclometasone dipropionate, halcinonide, mometasone furoate and fluocinolone acetonide.

36. A method according to claim 35 wherein the corticosteroid is selected from the group comprising hydrocortisone, betamethasone dipropionate, mometasone furoate and fluocinolone acetonide.

37. A method according to any one of claims 29 to 36, wherein the gold compound is auranofin.

DATED this 22nd Day of September 1998

MEDICAL INNOVATIONS LIMITED

Attorney: PAUL G. HARRISON
Fellow Institute of Patent Attorneys of Australia
of BALDWIN SHELSTON WATERS

PATENT COOPERATION TREATY

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Baldwin Shelston Waters
Level 21
60 Margaret Street
SYDNEY NSW 2000

RECEIVED
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BALDWIN SHELSTON WATERS

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing (day/month/year): 22 DEC 1998

Applicant's or agent's file reference
20276 IAR : ajw.wls

IMPORTANT NOTIFICATION

International application No.	International filing date	Priority date
PCT/AU 97/00747	4 November 1997	4 November 1996

Applicant
MEDICAL INNOVATIONS LIMITED et al

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translations to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide

Name and mailing address of the IPEA/AU	Authorized officer
AUSTRALIAN PATENT OFFICE PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No.: (02) 6285 3929	**R.L. POOLEY** Telephone No. (02) 6283 2242

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 20276 IAR : ajw.wls	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
International application No. **PCT/AU 97/00747**	International filing date *(day/month/year)* 4 November 1997	Priority Date *(day/month/year)* 4 November 1996
International Patent Classification (IPC) or national classification and IPC **Int. Cl.**[6] A61K 31/70, 31/28, 31/57, 31/58		
Applicant MEDICAL INNOVATIONS LIMITED et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of **5** sheets, including this cover sheet.

   [X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of **7** sheet(s).

3. This report contains indications relating to the following items:

I	[X]	Basis of the report
II	[ ]	Priority
III	[ ]	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	[ ]	Lack of unity of invention
V	[X]	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	[ ]	Certain documents cited
VII	[ ]	Certain defects in the international application
VIII	[X]	Certain observations on the international application

Date of submission of the demand 4 June 1998	Date of completion of the report 10 December 1998
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No. (02) 6285 3929	Authorized Officer **R.L. POOLEY** Telephone No. (02) 6283 2242

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/AU 97/00747

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed.

☒ the description, pages **1, 2, 6-24,** as originally filed,
pages , filed with the demand,
pages **3-5,** filed with the letter of **22 September 1998.**

☒ the claims, pages , as originally filed,
pages , as amended (together with any statement) under Article 19,
pages , filed with the demand,
pages **25-28,** filed with the letter of **22 September 1998.**

☒ the drawings, pages **1-2,** as originally filed,
pages , filed with the demand,
pages , filed with the letter of .

☐ the sequence listing part of the description:
pages , as originally filed
pages , filed with the demand
pages , filed with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, was on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages

☐ the claims, Nos.

☐ the drawings, sheets/fig

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report*

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	**30, 31, 32, 34**	**YES**
	Claims	**1-29, 33, 35, 36, 37**	**NO**
Inventive step (IS)	Claims		**YES**
	Claims	**1-37**	**NO**
Industrial applicability (IA)	Claims	**1-37**	**YES**
	Claims		**NO**

2. Citations and explanations (Rule 70.7)

NOVELTY (N) Claims 1-29, 33, 35-37

D1 AU 34351/89 (616755) B

D2 The Journal of Rheumatology, Volume 21, No.3, pages 435-441, Heytman et al, "The Longterm Effect of Pulsed Corticosteroids on the Efficacy and Toxicity of Chrysotherapy in Rheumatoid Arthritis"

D3 Journal of the American Veterinary Association, Volume 186, No.1, pages 59-66, Ihrke et al, "Pemphigus foloaceus in dogs: A review of thirty-seven cases"

D4 Journal of the American Academy of Dermatology, Volume 16, No.4, pages 845-854, Thomas et al, "Gold Therapy and its Indications in Dermatology"

D5 AU 15456/88 (604542)B

Documents D1-D5 all disclose combination treatment of various immune-mediated disorders with gold compounds and corticosteroids. The treatments of D2-D5 are disclosed to be adjunctive or to provide side-effect attenuation. However the psoriasis treatment of document D1 is stated to be synergistic, and this document discloses the presently preferred synergistic formulation of auranofin and betamethasone dipropionate.

Claim 29 and its dependent claims 33, 35, 36 and 37 are not distinguished from the disclosures of document D1. Claim i29 includes synergistic formulations of auranofin and betamethasone dipropionate by virtue of the disclosure of these formulations as preferred embodiments, and there is nothing in claim 29 to distinguish these claimed synergistic formulations from those of the document D1. Claim 29 as presently drafted appears to include mechanisms by which these formulations achieve synergy, but such mechanisms are incapable of conferring novelty on the formulations per se.

Claim 1 as presently drafted can still include the administration of compounds as alternative or adjunctive therapy, and consequently remains anticipated by documents D1-D5. The last line of the claim limits the compounds to exhibit equal action to each component of the disorder, but this action is not necessarily synergistic. Furthermore the synergistic action would be anticipated by document D1 which discloses synergistic treatments by the presently preferred compounds to the same locus (eg a psoriasis patient). The embodiments of the dependent claims of claim 1

continued

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 36 and 37 are incorrectly appended in that they are directed to method claims, but are appended to claims 35 and 29 which are composition claims.

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of : BOX V

are disclosed at various points throughout documents D1-D5 (eg the different modes of administration of the formulations). In addition claim 6 would not seem to be clearly differentiated from the disclosures of document D1, which includes synergistic compositions of a gold compound and one or more corticosteroids (eg betamethasone dipropionate and any other corticosteroid).

INVENTIVE STEP (IS) Claims 1-37

Claims 1-29, 33, 35-37 : as above

Claims 30, 31, 32, 34:

These claims merely involve the formulation of the composition of claim 29 for administration by various modes, and such formulation would be routine to a skilled person. The different formulation modes do not provide advantages which would be surprising or unexpected over the disclosed mode of topical administration.

INDUSTRIAL APPLICABILITY (IA) Claims 1-37

Claims 1-37 are industrially applicable.

Please note that claims 1-28 are subject matter of rule 67.1 (methods of treatment of humans) and as such do not require an international preliminary examination. However, because the subject matter does not contravene Australian law these claims have been examined.

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 31/70, 31/28, 31/57, 31/58

A1

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PO 3473 4 November 1996 (04.11.96) AU

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Published
With international search report.

(54) Title: SYNERGISTIC GOLD–CONTAINING COMPOSITIONS

(57) Abstract

This invention relates to a method of treating an immune–mediated disorder having one or more manifestations. The method comprises administering to a patient requiring such treatment a gold compound and at least one corticosteroid, wherein the at least one corticosteroid is selected to interact synergistically with the gold compound to exhibit preferential action towards one of the manifestations of said disorder or to exhibit equal action towards each manifestation of said disorder. The invention also relates to a pharmaceutical composition suitable for use in the method.

FOR THE PURPOSES OF INFORMATION ONLY

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TITLE: SYNERGISTIC GOLD-CONTAINING COMPOSITIONS

TECHNICAL FIELD

The present invention relates to pharmaceutical compositions comprising a gold compound in combination with a corticosteroid and their use in the treatment of dermatological disorders.

BACKGROUND OF THE INVENTION

The effectiveness of gold compounds in the treatment of rheumatoid arthritis has been known since the 1960s. More recently, gold complexes have been employed as therapeutic agents in the treatment of rheumatoid arthritis but their exact mechanism is still unknown. The most commonly used complexes have been water soluble, parenterally administered gold (Au(I)) thiolates such as aurothiomalate (Myocrisin®) and aurothioglucose (Solganol®). Subsequently, a number of alkylphosphine gold complexes displayed anti-arthritic activity when administered orally to adjuvant arthritic rats. Auranofin (1-thio-β-D-glucopyranose 2,3,4,6-tetraacetato-S)-(triethylphosphine)-Au(I)) was among the most potent and efficacious of the compounds tested and is now used in the treatment of rheumatoid arthritis in man.

Gold compounds have also been administered by intravenous and oral routes for the treatment of asthma, tuberculosis, pemphigus vulgaris, various forms of arthritis, cancer and infection. However, treatment with gold compounds has been frequently associated with unacceptable and on occasions serious side effects.

Corticosteroids have also found similar therapeutic applications. The success of topical corticosteroids in the therapy of inflammatory and proliferative disorders of the skin has led to vigorous development of new corticosteroids since their first topical use. An increase in potency has been achieved by chemical modification of the natural corticosteroid, hydrocortisone, without precise knowledge of the mechanism of action of corticosteroids. The development of more potent corticosteroids has extended their usefulness in a wide variety of skin diseases, but, especially with long term use, has led to unwanted effects. Systemic effects such as hypothalmic pituitary-adrenal-axis depression were already known from the systemic use of corticosteroids. Local side effects after topical application were observed only with the more potent synthetic steroids.

The most common serious side effects of topical corticosteroids are thinning of the skin, striae and telangiectasia. During long term treatment with very potent

corticosteroids, inflammatory cells are affected and the proliferation of keratinocytes and the activity of fibroblasts are also inhibited.

Fibroblasts synthesize important structural and functional components of the dermis, namely collagen, elastin and glycosaminoglycans. The inhibition of keratinocyte proliferation leads to thinning of the epidermis. Although the effect on the epidermis is usually reversible, the dermis can be irreversibly damaged.

Recently, topical formulations of gold organic complexes have found use in the treatment of skin disorders such as psoriasis. Thus, Australian Patent No. 616,755, describes the use of a topical formulation of auranofin in combination with a corticosteroid in the treatment of local inflammatory conditions such as those associated with psoriasis. In particular, treatment with a formulation comprising auranofin and betamethasone dipropionate demonstrated a remarkable synergy of action when compared to same concentrations of individual active ingredients. The finding that a gold compound can synergise with a corticosteroid enabled the use of considerably lower levels of both the gold compound and a corticosteroid in the formulations, thus enabling more effective therapy while obviating the well known side effects associated with the use of either gold compounds or corticosteroids alone.

Dermatological disorders are frequently associated with manifestations other than just inflammation. For example, psoriasis also contains a component of cellular hyperproliferation (hyperplasia), the mechanism of which is fundamentally different from that of inflammation and thus may not necessarily be affected by the topical gold/corticosteroid formulations. Furthermore, the inflammatory component of different dermatological conditions may range from very mild to very severe, necessitating variations in the formulation, in particular the choice of corticosteroid which would enable not only effective and appropriate treatment of the inflammatory component, but also provide the differential action in dermatological conditions where there is an additional component such as cellular hyperproliferation.

Other immune, autoimmune and infection disorders can also be associated with multiple manifestations, where effective treatment may rely on targeting only one of the manifestations of the disorder, or more than one, depending on the disorder treated and the assessment of the patient.

The present invention is based on a surprising finding that important differences exist between corticosteroids with respect to the degree of potentiation of effects and the

type of effect potentiated, when combined with a gold compound. That is to say, different corticosteroids, when combined with a gold compound, do not all have the expected similarity of synergistic action against inflammation and also demonstrate differential synergistic action with respect to inflammation and hyperplasia. In the compositions of the present invention certain corticosteroids synergise with the gold compound to provide a greater effect on the inflammatory component of a disorder, such as psoriasis, while other corticosteroids give rise to compositions with preferential effects on cellular hyperproliferation. It is contemplated that the compositions of the present invention could be effectively used also for the treatment of a variety of systemic, tissue-specific or localised immune, autoimmune and inflammatory disorders.

SUMMARY OF THE INVENTION

According to a first aspect the invention consists in a method of treating an immune-mediated disorder having one or more manifestations, comprising administering to a patient requiring such treatment a gold compound and at least one corticosteroid, wherein the at least one corticosteroid is selected to interact synergistically with the gold compound to exhibit preferential action towards one of the manifestations of said disorder or to exhibit equal action towards each manifestation of said disorder.

According to a second aspect the invention consists in a pharmaceutical composition comprising a gold compound and one or more corticosteroids, the corticosteroid being selected to interact synergistically with the gold compound to exhibit a differential action towards a specific manifestation of an immune-mediated disorder, in combination with a pharmaceutically acceptable carrier, excipient, adjuvant or solvent.

According to another aspect the present invention consists in a method of treating an immune-mediated disorder having one or more manifestations, comprising the step of administering to a patient requiring such treatment one or more compositions comprising a gold compound and one or more corticosteroids, wherein the corticosteroid is selected to provide a synergistic composition having preferential action towards one of the manifestations of said disorder.

According to another aspect the present invention consists in a method of treating an immune-mediated disorder having multiple manifestations, comprising the step of administering to a patient requiring such treatment one or more compositions comprising

a gold compound and one or more corticosteroids, wherein the corticosteroid is selected to provide a synergistic composition having preferential action towards one of the manifestations of said disorder.

According to another aspect the present invention consists in a method of treating an immune-mediated disorder having multiple manifestations, comprising the step of administering to a patient requiring such treatment one or more composition comprising a gold compound and one or more corticosteroids, wherein the corticosteroid is selected to provide a synergistic composition with equal action towards each manifestation of said disorder.

According to another aspect the present invention consists in a method of treating an immune-mediated disorder having one or more manifestations, comprising the step of administering to a patient requiring such treatment a composition comprising a gold compound and one or more compositions comprising one or more corticosteroids wherein the corticosteroid is selected to provide a synergistic composition with preferential activity towards one of the manifestations of said disorder and wherein the composition comprising a gold compound is administered orally and the one or more compositions comprising one or more corticosteroids is administered topically, in amounts effective to provide a synergistic composition of gold and a corticosteroid having preferential action towards said manifestation.

Preferably the manifestations of the immune-mediated disorder comprise an inflammatory component and a cellular hyperproliferation component and the composition comprises at least two corticosteroids, one of which is selected to provide a synergistic composition with preferential action towards the inflammatory component and the second corticosteroid is selected to provide a synergistic composition with preferential action towards the cellular hyperproliferation component of said disorder.

Preferably the disorder to be treated is an immune-mediated dermatological disorder which is associated with more than one manifestation. Examples of immune-mediated dermatological disorders include psoriasis or dermatitis such as contact, atopic or seborrheic dermatitis. Other disorders include rheumatoid arthritis. Typical manifestations include an inflammatory component and/or a cellular hyperproliferation component. The cellular hyperproliferation component can further manifest as cellular hyperplasia. The corticosteroid can be selected to provide a synergistic composition with activity towards cellular hyperproliferation in preference to inflammation or vice

versa. Such a corticosteroid can be selected from, for example, the group consisting of betamethasone dipropionate and fluocinolone acetonide. In cases where inflammation needs to be targeted in preference to cellular hyperproliferation, the corticosteroid is preferably selected from the group consisting of mometasone furoate and betamethasone dipropionate.

The composition is suitably formulated for topical administration.

Where the immune-mediated disorder is characterised by a number of different manifestations, the preferred method of treatment could employ one or more compositions comprising a gold compound and one or more corticosteroids, wherein the corticosteroids are selected to provide composition(s) with preferential activity towards only one of the manifestations of said disorder. Thus the treatment of each individual manifestation is achieved through use of composition(s) comprising one or more selected corticosteroids, which may be applied in the form of two or more separate compositions or a single composition comprising two or more corticosteroids.

Preferably the gold compounds used in the present invention are lipid soluble. Even more preferably the gold compounds used are formulated for topical application. However, it will be understood that systemically or locally administered compositions are also within the scope of the present invention including those administered by injection, preferably intra-articularly. In this regard the corticosteroid can be formulated for oral, topical, systemic or local administration.

According to another aspect the present invention consists in a pharmaceutical composition comprising a gold compound and one or more corticosteroids, the corticosteroid being selected to provide a synergistic composition with a differential action towards a specific manifestation of an immune-mediated disorder, in combination with a pharmaceutically acceptable carrier, excipient, adjuvant or solvent.

Preferably the gold compound is auranofin and the corticosteroid is selected from the group comprising hydrocortisone acetate, hydrocortisone, betamethasone, dexamethasone, fluocortolone 21-pivalate, triamcinolone acetonide, betamethasone valerate, alclometasone dipropionate, halcinonide, betamethasone dipropionate, mometasone furoate or fluocinolone acetonide. More preferably the corticosteroid is selected from the group comprising hydrocortisone, betamethasone dipropionate, mometasone furoate or fluocinolone acetonide.

BRIEF DESCRIPTION OF FIGURES

Figure 1: A histogram showing the effects of auranofin and glucocorticoids alone or in combination on TPA-induced epidermal hyperplasia. BMD: betamethasone dipropionate; HYD: hydrocortisone; FA: fluocinolone acetonide, MMF: mometasone furoate; AF: auranofin. Bars indicate standard error of the mean (SEM).

Figure 2: A histogram showing the effects of auranofin and glucocorticoids alone or in combination on TPA-induced inflammatory cell infiltration. BMD: betamethasone dipropionate; HYD: hydrocortisone; FA: fluocinolone acetonide; MMF: mometasone furoate; AF: auranofin. Bars indicate standard error of the mean (SEM).

DESCRIPTION OF THE PREFERRED EMBODIMENT

For convenience, a TPA (12-*O*-tetradecanoylphorbol 13-acetate), model of psoriasis, as an example of an immune-mediated disorder which has an inflammatory as well as a cellular hyperproliferation component, will be used to demonstrate differential action of different corticosteroids as well as differential action of different formulations of a gold compound and a corticosteroid.

Although psoriasis does not occur in animals other than humans, studies have shown that the application of TPA produces an inflammatory reaction with epidermal thickening that resembles psoriasis in many ways. It produces epidermal hyperplasia and inflammatory cell infiltration into the dermis, both of these features are also characteristic of psoriasis.

TPA increases the activity of the phospholipase C/inositol trisphosphate/ diacylglycerol system. This system activates the protein kinase C and arachidonic acid pathways. Both these systems have been implicated in the pathogenesis of psoriasis. TPA-treated mouse is believed to be a suitable model for psoriasis. This animal model will be used to show differential actions of different corticosteroids and the synergistic effects of compositions comprising a gold compound and a corticosteroid.

Three parameters have been measured: skin-fold thickness, epidermal hyperplasia and inflammatory cell infiltration into the dermis. These features, particularly the last two, are the hallmarks of psoriasis. It is noteworthy however, that the current findings clearly have implications beyond mere treatment of dermatological disorders. Systemic or tissue inflammatory and hyperplastic conditions could also benefit from treatment with the compositions of the present invention.

Topical Corticosteroids

Topical corticosteroids can be grouped according to their strength: weak, medium, strong and very strong. Vasoconstriction assay is considered the best method of assessing the potency of various preparations. It is not known whether the measurement of vasoconstriction predicts anti-inflammatory activity. Other methods of assaying that are available include clinical trial, dermal thickness radiograph, biopsy for assessing epidermal thinning, and mitotic inhibition assays.

A useful clinical guide to the relative potencies of topical corticosteroid preparations is shown in Table 1, the rank order arrangement being approximately the same for ointments and creams. The preparations in each group are only roughly equipotent.

Table 1 **A guide to the clinical potencies of topical corticosteroids**

Weak	Medium	Strong	Very Strong
Dexamethasone 0.01%	Alclometasone dipropionate 0.05%	Amcinonide 0.1%	Beclomethasone dipropionate 0.5%
Fluocinolone acetonide 0.0025%	Betamethasone valerate 0.025%	Beclomethasone dipropionate 0.025%	Clobetasol propionate 0.05%
Hydrocortisone 0.5% and 0.1%	Clobetasone butyrate 0.05%	Betamethasone benzoate 0.025%	Diflucortolone valerate 0.3%
Hydrocortisone acetate 1%	Dexamethasone 0.05%	Betamethasone dipropionate 0.05%	Fluocinolone acetonide 0.2%
Methylprednisolone acetate 0.25%	Flumethasone pivalate 0.02%	Betamethasone valerate 0.1%	
	Fluocinolone acetonide 0.01%	Budesonide 0.025%	
	Fluocortin butylester 0.75%	Desonide 0.05%	
	Fluocortolone 0.2%	Dexamethasone 0.25%	
	Flurandrenolone 0.0125%-0.025%	Diflorasone diacetate 0.05%	
	Hydrocortisone 1% with urea	Diflucortolone valerate 0.1%	
		Fluclorolone acetonide 0.025%	
		Fluocinolone acetonide 0.025%	
		Fluocinonide 0.05%	
		Fluocortolone 0.5%	
		Fluprednidene acetate 0.1%	
		Flurandrenolone 0.05%	
		Halcinonide 0.1%	
		Hydrocortisone butyrate 0.1%	
		Mometasone furoate 0.1%	
		Triamcinolone acetonide 0.1%	

The invention will now be more particularly described with reference to specific embodiments by way of non-limiting example only.

Example 1: Animal treatment and methods of measurement

Materials

Auranofin was kindly donated by Smith Kline and Beecham Pharmaceuticals, King of Prussia, Philadelphia, USA.

Alclometasone dipropionate, betamethasone dipropionate, betamethasone valerate, betamethasone (as free alcohol) and mometasone furoate were kindly donated by Schering-Plough Pty. Ltd., Baulkham Hills, NSW, Australia.

Halcinonide, Hydrocortisone and Triamcinolone acetonide were kindly donated by Bristol-Myers Squibb Pharmaceuticals Pty. Ltd.

Dexamethasone was kindly donated by Roussel Uclaf, Paris, France.

Fluocortolone 21-pivalate was kindly donated by Schering AG, Berlin, Germany.

12-*O*-Tetradecanoylphorbol 13-acetate, fluocinolone acetonide, aluminium potassium sulphate, sodium hydrogen carbonate, sodium iodate, magnesium sulphate, eosin Y, phloxine, calcium carbonate, formaldehyde acetic acid (17 M), thymol, xylene, haematoxylin and "Paraplast" tissue embedding medium were obtained from Sigma Chemical Company, Castle Hill, NSW, Australia.

Sorbolene cream A.P.F. was obtained from Wille Laboratories, Carole Park, Queensland, Australia.

Preparation of auranofin 0.2 % solution

Auranofin (20 mg) was dissolved in 10 mL of acetone to give the strength 0.2%. Auranofin solution was freshly prepared for each experiment.

Preparation of auranofin ointment

Various strengths of auranofin ointment were made according to the formula as shown below:

strength (% w/w)	auranofin	propylene glycol (10%)	white soft paraffin
0.20	40 mg	2 g	to 20 g
0.50	100 mg	2 g	to 20 g

Methods of animal treatment

Female BALB/c mice aged 6 to 8 weeks were obtained from the University of Sydney, and treated according to a protocol approved by the University of Sydney Animal Care and Ethics Committee.

The mice were housed in stainless steel cages, 6 mice per cage under normal laboratory conditions (room temperature at about 22°C) at least 7 days before the experiments for acclimatization. Food and water were allowed *ad libitum* throughout the experiment period. The backs of the mice were shaved with an electric clipper two days before each treatment and only those mice showing no hair regrowth were used (i.e., the mice in the resting phase of the hair growth cycle were selected). During treatment, the mice were held with their tails and put on top of the cage so that they grasped the cage and rested there. The solutions were applied to an area approximately 2 cm x 2 cm on the shaved back of the mice by using a "Pipetman" to apply the solution. If auranofin ointment or ointment base was applied, the amount was standardized by using a microspatula which was crimped at one end, the ointment was then put into the ridge and the excess removed by means of another microspatula and applied sparingly twice a day. After a fixed time, the mice were killed routinely by cervical dislocation between 9 a.m. and 11 a.m. to avoid variations due to circadian rhythms, and an area (1 cm x 1 cm) was excised from the centre of the treated area by scalpel and scissors. The rest of the tissues were disposed by combustion. The tissues were then fixed, embedded, sectioned and stained.

Methods of preparation of skin sections

The method of preparation of skin sections was adapted from a method developed by the Department of pathology, University of Sydney and shown to be successful.

Fixation, embedding, sectioning and staining

Standard preparation procedures were used. Briefly, the tissue was fixed in 10% buffered formalin for 24 hours, washed in tap water for 10 minutes and then processed in an automatic tissue processor (Tissue-Tek VIP 200). In the automatic tissue processor, the tissue was dehydrated in a graded series of alcohol and xylene at room temperature, and was then infiltrated with 4 changes of paraffin wax ("Paraplast" tissue mounting medium) at 60°C. It was finally embedded in fresh paraffin wax.

Sections 5 μm thick were cut on an American Optical Spencer "820" microtome. The sections were then mounted on clean microscope slides using wood glue ("Selleys" Aquadhere, 1:100 dilution with water) as adhesive, and were allowed to dry in an oven at 45°C for at least 2 hours (usually overnight).

After the sections were blued in the Scott's blueing solution, they were examined under microscope to assess that nuclei were clearly stained and cytoplasm was unstained.

Measurement of skin-fold thickness

The back skin of shaved mice was folded and measured by using a "Etalon" micrometer screw gauge. One measurement was taken for each mouse.

Measurement of epidermal thickness

Epidermal thickness was determined by image analysis. This image analysis system was a minicomputer (Tracor Northern TN8500) attached to a light microscope (Zeiss Axioplan) and a camcorder (Sony DXC-3000P). Sections were taken from each tissue block and 20 measurements were taken at fixed intervals from each section. The average value for the 20 measurements was obtained and entered as one value for each mouse. The mean and SEM for the six mice in each treatment group were calculated.

Measurement of infiltration of inflammatory cells

Infiltration of inflammatory cells was determined by the same image analysis system using the section taken from the block of mouse skin embedded in paraffin wax or Spurr's resin and stained with haematoxylin and eosin or toluidine blue respectively. For each section, 10 fields. unless otherwise stated, were chosen randomly and the cell density per mm^2 of field determined. The average value for the 10 fields was obtained and entered as one value for each mouse. The mean and SEM for the six mice in each treatment group were calculated.

The measurement of the inflammatory cell infiltration included the background values which included other materials in the dermis stained in the same way. However, the increase, if there is any, reflects the migration of inflammatory cells.

Data treatment

The per cent inhibition of drug on TPA-induced skin responses (i.e., epidermal hyperplasia, inflammatory cell infiltration and skin-fold thickness) was calculated by using the following formula:

$$\text{Per cent inhibition} = \frac{\text{Total response due to TPA} - \text{Total response due to drug}}{\text{Total response due to TPA} - \text{Total response due to acetone}} \times 100\%$$

It is commonly found that the relationship between dose (or concentration) and response may be satisfactorily described using the Michaelis Menton equation or a variant of it such as the Hill equation. This provides estimates of (a) the potency, (b) the efficacy or maximum effect (E_{max}) and the slope of the log concentration-response curve by using Hill coefficient (γ). The Hill Equation may be expressed as follows:

$$E = \frac{Emax \times C^{\gamma}}{IC_{50}^{\gamma} + C^{\gamma}}$$

where IC_{50} is the drug concentration producing 50% of the maximal response and E_{max} refers to the maximal effect produced by the drug and is also termed efficacy. Efficacy is the measurement of the intrinsic ability of a drug to initiate a response once it occupies receptor sites. Measurement of both the E_{max} and the IC_{50} (potency) are clearly crucial when comparing the activity of similar drugs. The Hill coefficient (γ) measures the slope of the dose-effect curve which can be markedly influenced by the shape of the curve that describes the binding of the drug to the receptor. For many drugs, γ lies between 0.6 and 1.5. The use of the Hill coefficient not only improves the fit of the data, but also indicates the influence of changes in dose or concentration on response: for example, when γ is greater than 1, the slope is very steep, meaning that a marked change in drug effect is associated with a small change in dose or concentration of drug. On the other hand, when γ is less than 1, with a shallow hyperbolic concentration effect relationship, the activity occurs over a wide range of drug levels. Hence, the different values of γ can dramatically affect the drug's clinical usefulness

In the present study, concentration-response curves were obtained for a series of corticosteroids. In these experiments, curve fitting was accomplished using a computer programme called "The Scientist" (MicroMath Scientific Software, Salt Lake City, Utah, USA.) in which the parameters, E_{max}, IC_{50} and Hill coefficient (γ) for each steroids were estimated by using non-linear regression and least square fits.

The overall significance of differences between treatments was determined by one way analysis of variance, while the Tukey HSD test was used to examine the significance level of specific contrasts. The Systat for Windows program (Systat Inc, Evanston, Illinois, USA.) was used.

Example 2: Effects of TPA on skin of mice

This study was conducted to determine the time course of effects produced by applying TPA to mice and killing at intervals of 1, 2, 3, 5 and 8 days. Peak times for

epidermal hyperplasia, dermal inflammation and skin-fold thickness were determined. The object of this study was to determine the best time to sacrifice TPA-treated mice so as to obtain the maximum response to TPA. The literature indicates that TPA-induced epidermal hyperplasia and dermal inflammation peak at different times. It was thus expected that a compromise time would have to be selected.

Forty two female BALB/c strain mice were divided into the treatment groups and the mice were treated with a single application (100 µL) of TPA (0.01% in acetone) and sacrificed at days 1, 2, 3, 5 and 8 and the time course of TPA effects on epidermal hyperplasia, dermal inflammatory cell infiltration and skin-fold thickness measured as described in Example 1.

The skin responses to TPA are summarized below:

	Day 1	Day 2	Day 3	Day 5	Day 8
Increase in epidermal thickness	326%	382%	393%	270%	130%
Increase in dermal inflammatory cell density	397%	296%	272%	280%	225%
Increase in skin-fold thickness	193%	142%	124%	116%	107%

The experiment showed that a single application of TPA caused epidermal thickening, dermal inflammation and an increase in skin-fold thickness that lasted for at least 8 days. The peak effects were observed at 72 hours for epidermal hyperplasia and at 24 hours for dermal inflammation and skin-fold thickening.

Based on these results it was decided that an appropriate compromise, for most experiments, would be to sacrifice the animals 24 hours after a single application of TPA. This would result in maximum effects for inflammation and skin-fold thickness and near maximum effects for epidermal hyperplasia (over 80% of peak effect). Unless otherwise stated, mice were sacrificed 24 hours after the application of TPA.

Example 3: Action of Different Corticosteroids

In the first instance the ability of corticosteroids alone to inhibit TPA lesions was investigated. The following groups of corticosteroids were tested (the classification of the potencies of corticosteroids is dependent on the concentration used, the composition of the vehicle and the effect being studied) (Table 1).

Low potency: betamethasone, dexamethasone, hydrocortisone, hydrocortisone acetate.

Medium potency: alclometasone dipropionate, fluocortolone 21-pivalate.

High potency: betamethasone dipropionate, betamethasone valerate, fluocinolone acetonide, halcinonide, mometasone furoate, triamcinolone acetonide

Mice were divided into treatment groups. TPA and corticosteroids were premixed to the concentrations required and applied to the backs of mice immediately. For those steroids not very soluble in acetone (i.e., betamethasone, dexamethasone, hydrocortisone and hydrocortisone acetate), the drugs were dissolved in 100 μL dimethylformamide before further dilution with acetone. The efficacy of corticosteroids in inhibiting epidermal hyperplasia, inflammatory cell infiltration and skin-fold thickness was assessed as described previously. Concentration-response curves were determined after computer-fitting of data. The curve fitting technique was generated by a computer programme called "The Scientist" in which the parameters in the Hill Equation were generated. These included E_{max}, IC_{50}, and the Hill coefficient (γ) for each steroid. Concentration-response curves for each steroid were plotted and the relative potencies were determined from the IC_{50} values. Comparisons were made of variations in ratios of IC_{50} for each corticosteroids tested. These values were compared with those in the literature and reflected the relative intrinsic potencies of steroids.

Table 2 **A summary of the concentration-response curves for inhibition of TPA-induced epidermal hyperplasia by various steroids showing the values of E_{max}, IC_{50} and gamma (γ) with respect to the Hill equation.**

Corticosteroids	E_{max} (% inhibition)	IC_{50} ($M \times 10^{-4}$)	Gamma (γ)
Alclometasone dipropionate	96.59 ± 7.90 (76.28-116.90)	0.89 ± 0.30 (0.16-1.67)	0.67 ± 0.12 (0.36-0.97)
Betamethasone	94.19 ± 7.33 (75.35-113.04)	13.81 ± 3.73 (4.22-23.39)	0.81 ± 0.11 (0.51-1.10)
Betamethasone dipropionate	95.59 ± 6.55 (82.14-109.04)	0.81 ± 0.36 (0.49-1.13)	0.54 ± 0.06 (0.37-0.71)
Betamethasone valerate	82.24 ± 2.84 (75.69-88.78)	0.15 ± 0.02 (0.10-0.20)	0.94 ± 0.12 (0.66-1.21)
Dexamethasone	90.70 ± 5.72 (76.72-104.69)	1.26 ± 0.44 (0.85-1.67)	0.50 ± 0.08 (0.31-0.69)
Fluocinolone acetonide	89.60 ± 6.93 (70.36 ± 108.85)	0.39 ± 0.14 (0.043-0.78)	0.75 ± 0.23 (0.12-1.38)
Fluocortolone 21-pivalate	85.18 ± 9.51 (58.79-111.58)	0.40 ± 0.15 (0.12-0.68)	0.97 ± 0.30 (0.13-1.82)
Halcinonide	92.55 ± 2.98 (85.25-99.85)	0.97 ± 0.13 (0.66-1.27)	0.78 ± 0.06 (0.62-0.94)
Hydrocortisone	99.04 ± 9.54 (72.56-125.51)	46.18 ± 13.22 (9.47-82.90)	0.96 ± 0.17 (0.49-1.44)
Hydrocortisone acetate	79.63 ± 7.62 (60.04-99.23)	36.67 ± 12.01 (5.80-67.56)	0.79 ± 0.13 (0.46-1.13)
Mometasone furoate	83.31 ± 3.04 (76.11-90.51)	0.23 ± 0.04 (0.14-0.33)	0.79 ± 0.11 (0.53-1.04)
Triamcinolone acetonide	89.80 ± 6.40 (74.14-105.46)	1.13 ± 0.35 (0.28-1.98)	0.75 ± 0.15 (0.39-1.11)

Results are presented as means ± SD. Figures in brackets are confidence intervals

Table 3 **A summary of the concentration-response curves for inhibition of TPA-induced inflammatory cell infiltration by various steroids showing the values of E_{max}, IC_{50} and gamma (γ) with respect to the Hill equation.**

Corticosteroids	E_{max} (% inhibition)	IC_{50} ($M \times 10^{-8}$)	Gamma (γ)
Alclometasone dipropionate	82.12 ± 5.65 (67.58-96.66)	0.32 ± 0.09 (0.10-0.54)	0.97 ± 0.26 (0.31-1.63)
Betamethasone	74.55 ± 3.29 (66.09-83.01)	13.12 ± 1.65 (8.87 ± 17.37)	1.28 ± 0.17 (0.85-1.71)
Betamethasone dipropionate	90.77 ± 3.71 (83.18-98.37)	0.29 ± 0.06 (0.16-0.41)	0.52 ± 0.06 (0.39-0.65)
Betamethasone valerate	73.52 ± 1.76 (69.46-77.57)	0.29 ± 0.03 (0.22-0.34))	0.93 ± 0.07 (0.77-1.09)
Dexamethasone	99.05 ± 10.98 (72.18-125.93)	4.44 ± 1.02 (3.19-5.69)	0.73 ± 0.19 (0.25-1.20)
Fluocinolone acetonide	79.60 ± 2.41 (74.05-85.15)	0.16 ± 0.02 (0.11-0.21)	1.05 ± 0.14 (0.72-1.38)
Fluocortolone 21-pivalate	97.91 ± 12.16 (64.15 ± 131.67)	1.10 ± 0.40 (0.55-1.65)	0.94 ± 0.21 (0.36-1.54)
Halcinonide	90.34 ± 6.29 (74.94-105.74)	0.31 ± 0.05 (0.14-0.48)	0.60 ± 0.11 (0.32-0.88)
Hydrocortisone	100.29 ± 9.36 (71.35-129.23)	61.48 ± 9.66 (39.13-83.83)	0.57 ± 0.26 (0.25-0.89)
Hydrocortisone acetate	79.36 ± 11.49 (59.39-99.33)	77.33 ± 13.85 (60.28-94.58)	1.11 ± 0.27 (0.42-1.80)
Mometasone furoate	89.98 ± 4.88 (78.45-101.51)	0.20 ± 0.05 (0.08-0.33)	0.69 ± 0.14 (0.37-1.01)
Triamcinolone acetonide	77.24 ± 1.26 (74.15-80.33)	0.39 ± 0.03 (0.33-0.46)	1.42 ± 0.11 (1.14-1.70)

Results are presented as means ± SD. Figures in brackets are confidence intervals

Tables 2 and 3 provide an estimate of the efficacies (E_{max}), potencies (IC_{50}) and slope of the concentration-response curve (γ) for the 12 corticosteroids investigated in this study. These values were obtained from the Hill equation which is a modified form of the Michaelis-Menton equation.

The apparent excellent correlations between IC_{50} values could indicate that inhibition of inflammation and epidermal hyperplasia are mediated by the same mechanism or else that the limiting factor in producing the two effects was the ability of the steroid to penetrate the skin. The fact that the maximum effects (E_{max}) and slopes (γ) of the concentration-response curves for the two effects were very poorly correlated suggests that different mechanisms are involved in suppressing inflammation and epidermal hyperplasia by the steroids. In addition, the correlations between IC_{50} values are not so impressive when the effects of certain outlier drugs are removed. The effect of removing outliers is shown in Table 4:

Table 4: IC_{50} values (inflammation vs epidermal hyperplasia)

Plot of IC_{50} values (inflammation vs epidermal hyperplasia)	**r** (derived from Hill equation)	**r** (read from graph where IC_{50} = concentration that inhibits half the effect of TPA)
All drugs included	0.961 ($p<0.0005$)	0.909 ($p<0.0005$)
Hydrocortisone and hydrocortisone acetate not included	0.959 ($p<0.0005$)	o.988 ($p<0.0005$)
Hydrocortisone, hydrocortisone acetate, betamethasone dipropionate, dexamethasone and fluocortolone 21-pivalate not included	0.741 ($p = 0.057$)	0.637 ($p = 0.072$)

From the above results it seems likely that the steroids inhibit the inflammatory and hyperplastic effects of TPA by different mechanisms, either inducing different biochemical responses or producing the same response in different cell lines. This conclusion is very relevant to the possible synergistic effects of auranofin are described.

The determination of E_{max} values from the Hill equation could be subject to error due to some uncertainty about measurements made at the top of the concentration-

response curves. Therefore, IC_{50} values were determined by two methods: (a) using the E_{max} value generated from the Hill equation (Tables 5 and 6), and (b) directly from the concentration-response curve, taking the IC_{50} value as that concentration that inhibited 50% of the TPA-induced hyperplasia and inflammation (Tables 7 and 8). The difference between IC_{50} values, and hence relative potencies, determined by the two methods was not great. However, direct reading from the concentration-response curve was considered more reliable and these readings were used for calculating the "synergistic factors" given in Tables 9 and 10.

Table 5 **Actual and relative potencies of topical corticosteroids for inhibition of TPA-induced epidermal hyperplasia [values generated from the Hill equation where IC_{50} is the concentration that produced 50% of the maximum inhibitory effect (E_{max})].**

Corticosteroids	IC_{50} for inhibition of epidermal thickening ($M \times 10^{-4}$)	Relative potency
Hydrocortisone acetate	36.67	1.0
Hydrocortisone	46.18	0.79
Betamethasone	27.25	1.35
Dexamethasone	1.26	29.10
Triamcinolone acetonide	1.13	32.45
Halcinonide	0.97	37.80
Alclometasone dipropionate	0.89	41.20
Betamethasone dipropionate	0.81	45.27
Fluocortolone 21-pivalate	0.4	91.68
Fluocinolone acetonide	0.39	94.03
Mometasone furoate	0.23	159.43
Betamethasone valerate	0.15	244.47

Table 6 **Actual and relative potencies of topical corticosteroids for inhibition of TPA-induced inflammatory cell infiltration into the dermis [values generated from the Hill equation where IC_{50} is the concentration that produced 50% of the maximum inhibitory effect (E_{max})].**

Corticosteroids	IC_{50} for inhibition of inflammatory cell infiltration in the dermis ($M \times 10^{-4}$)	Relative potency
Hydrocortisone acetate	77.33	1.0
Hydrocortisone	61.48	1.26
Betamethasone	13.12	5.89
Dexamethasone	4.44	17.42
Fluocortolone 21-pivalate	1.10	70.30
Triamcinolone acetonide	0.39	198.28
Alclometasone dipropionate	0.32	241.66
Halcinonide	0.31	249.45
Betamethasone dipropionate	0.29	266.66
Betamethasone valerate	0.29	266.66
Mometasone furoate	0.20	386.65
Fluocinolone acetonide	0.16	483.31

Table 7 **Actual and relative potencies of topical corticosteroids for inhibition of TPA-induced epidermal hyperplasia (values taken from concentration-response curve where IC_{50} is the concentration that inhibited 50% of the TPA effect).**

Corticosteroids	IC_{50} for inhibition of epidermal thickening ($M \times 10^{-4}$)	Relative potency
Hydrocortisone acetate	70.00	1.0
Hydrocortisone	45.10	1.55
Betamethasone	50.00	1.40
Dexamethasone	2.00	35.0
Triamcinolone acetonide	1.40	50.0
Betamethasone dipropionate	1.40	50.0
Halcinonide	1.10	63.64
Alclometasone dipropionate	1.00	70.0
Fluocortolone 21-pivalate	0.60	116.67
Mometasone furoate	0.40	175.0
Betamethasone valerate	0.22	318.18
Fluocinolone acetonide	0.21	333.33

Table 8 **Actual and relative potencies of topical corticosteroids for inhibition of TPA-induced inflammatory cell infiltration into the dermis (values taken from concentration-response curve where IC_{50} is the concentration that inhibited 50% of the TPA effect).**

Corticosteroids	IC_{50} for inhibition of inflammatory cell infiltration in the dermis ($M \times 10^{-4}$)	Relative potency
Hydrocortisone acetate	110.0	1.0
Hydrocortisone	60.0	1.83
Betamethasone	21.0	5.23
Dexamethasone	4.10	26.83
Fluocortolone 21-pivalate	1.10	100.0
Triamcinolone acetonide	0.70	157.14
Betamethasone valerate	0.65	169.23
Alclometasone dipropionate	0.60	183.33
Halcinonide	0.60	183.33
Betamethasone dipropionate	0.40	275.0
Mometasone furoate	0.30	366.67
Fluocinolone acetonide	0.25	440.0

In the present study, hydrocortisone, hydrocortisone acetate, betamethasone and dexamethasone had low to medium potencies with respect to both inhibition of TPA-induced epidermal hyperplasia and TPA-induced inflammatory cell infiltration. This ranking was consistent with corresponding potencies in clinical setting that was shown in Table 1.

Halcinonide, triamcinolone acetonide, alclometasone dipropionate, betamethasone dipropionate, fluocortolone 21-pivalate were found to have medium to strong potencies in inhibition of TPA-induced epidermal hyperplasia and inflammatory cell infiltration, and these values were consistent with the clinical potencies.

Finally, mometasone furoate, betamethasone valerate, betamethasone dipropionate, and fluocinolone acetonide had strong to very strong potencies for TPA-induced epidermal hyperplasia. Amongst them, betamethasone valerate was shown to be the most potent agent. When their potencies for inhibition of TPA-induced inflammatory cell infiltration were investigated, they were also shown to have strong to very strong anti-inflammatory effect. Fluocinolone acetonide was found to be the most potent agent, with a relative potency of 483 (Table 6) or 440 (Table 8).

When comparisons were made between the relative potencies of the steroids tested in this study and their respective clinical potencies, the order of potency was generally the same.

It might be expected that a particular corticosteroid would have equal potency with respect to anti-hyperplastic and anti-inflammatory actions. Our results showed that these reactions were not necessarily closely related. Linear regression of the relative potencies for inhibition of the hyperplastic effects of the steroids vs relative potencies for suppression of inflammation gave a value $r = 0.573$ ($p = 0.51$) for data from tables 5 and 6 and a value of $r = 0.658$ ($p < 0.02$) for values in tables 7 and 8. Thus, about 65% of the variance between the two actions seems to be due to some common property (which could be lipid solubility) but a significant component of these actions differs with respect to suppression of hyperplasia and suppression of inflammation. This is also illustrated by comparing the rank orders of potency in Tables 7 and 8. Only six of the 12 steroids have the same rank for both effects and, of these steroids, four are the four least potent.

Example 2: Synergistic Effect Of Auranofin And Corticosteroids With Different Clinical Potencies

Results of preliminary studies indicated that auranofin, under certain conditions, can inhibit some of the effects of TPA, although it is not particularly potent in this regard.

The present study examines whether combinations of auranofin and corticosteroids had a synergistic effect in suppressing TPA lesions.

Four corticosteroids with different clinical potencies ranging from weak to strong were chosen, namely, hydrocortisone, fluocinolone acetonide, betamethasone dipropionate and mometasone furoate. TPA was premixed with the corticosteroids in the presence or absence of a fixed concentration of auranofin (0.2%) to produce the required concentrations and applied to the backs of mice immediately. Concentration-response curves were determined by non-linear regression using least squares fitting. IC_{50} values were determined by reading the value from the graph that corresponded to 50% of the effect produced by TPA (Tables 9 and 10).

The term 'apparent IC_{50}' refers to the value for the combination of steroid and auranofin.

Table 9 **Apparent IC_{50} values obtained from the computer fitted graph for the effects on TPA-induced epidermal hyperplasia of four corticosteroids in the absence and presence of auranofin (0.2%).**

	Apparent IC_{50} ($M \times 10^{-4}$)		
Corticosteroids	**without auranofin**	**with auranofin**	**Synergistic factor**
Betamethasone dipropionate	1.40 ± 0.36	0.025 ± 0.003	56.0
Hydrocortisone	45.00 ± 13.22	22.00 ± 11.23	2.05
Fluocinolone acetonide	0.21 ± 0.14	0.016 ± 0.002	13.13
Mometasone furoate	0.40 ± 0.04	0.31 ± 0.05	1.29

Results are presented as means ± SD.

Table 10 **Apparent IC_{50} values obtained from the computer fitted graph for the effects on TPA-induced dermal inflammatory cell infiltration of four corticosteroids in the absence and presence of auranofin (0.2%).**

	Apparent IC_{50} ($M \times 10^{-4}$)		
Corticosteroids	**without auranofin**	**with auranofin**	**Synergistic factor**
Betamethasone dipropionate	0.40 ± 0.06	0.090 ± 0.016	4.44
Hydrocortisone	60.00 ± 9.66	31.00 ± 4.12	1.94
Fluocinolone acetonide	0.25 ± 0.002	0.11 ± 0.013	2.27
Mometasone furoate	0.30 ± 0.05	0.008 ± 0.001	37.50

Results are presented as means ± SD.

The value termed the 'synergistic factor' is defined as the IC_{50} value for the steroid determined in the absence of auranofin divided by the IC_{50} for the same steroid determined in the presence of auranofin (0.2%).

Synergism refers to situations in which a combination of two drugs produces an effect that is significantly greater than the algebraic sum of the effects when the same dose or concentration of each drug is observed separately in the same test system. Synergism can result in a multifold potentiation of the effects of one or both drugs or it can give rise to effects that are qualitatively different from those elicited by the drugs when used separately.

With respect to effects on epidermal hyperplasia, only two of the four steroids tested could be regarded as showing a synergistic reaction with auranofin, namely betamethasone dipropionate and fluocinolone acetonide. From results depicted in Tables 9 and 10 it can be seen that in the case of betamethasone dipropionate and fluocinolone acetonide, the per cent increase in the apparent potencies of the steroids is 5,600% and 1,300%, respectively. However, in the case of the least potent of the four steroids, namely, hydrocortisone, the apparent increase in potency was 100%. A more effective

way of demonstrating the presence of true synergism is to compare separately the following:

1) auranofin (0.2%) alone,
2) a low concentration of steroid alone (sufficient to inhibit about 20% of the effects of TPA — this value can be read from the concentration-response curve for the steroid when studied alone),
3) the same concentration of steroid as in (2) combined with auranofin (0.2%) — this value can be obtained from the dose-response curve for steroid in the presence of auranofin, and
4) a concentration of the same steroid used in (2) but in sufficient concentration as to produce the same effect as that achieved in (3).

If the effects of (3) appear to be the summation of (1) and (2), the result is not synergism. If the effects of (3) greatly exceed those of (1) and (2) if added arithmetically, the result is synergism according to our definition.

The results for epidermal hyperplasia are displayed in Figure 1. Auranofin alone inhibited TPA-induced epidermal hyperplasia by about 10% in all four studies. Betamethasone dipropionate 1×10^{-5} M alone caused about 20% inhibition of TPA effect. The combination of betamethasone dipropionate (1×10^{-5} M) and auranofin (0.2%) produced about 65% inhibition of TPA effect. To gauge the significance of the increased effect that resulted when auranofin was added to betamethasone dipropionate, comparison should be made with the concentration of betamethasone dipropionate that, in the absence of auranofin, produced the same effect. This value was 5×10^{-4} M or 50 times the concentration that produced the same effect in the presence of auranofin.

With respect to epidermal hyperplasia, the studies demonstrate that: (a) a massive synergism results when auranofin is added to betamethasone dipropionate and to fluocinolone acetonide; (b) a minor degree of synergism may result from the combination of hydrocortisone and auranofin; and (c) that no synergism or even additive effect results when auranofin is co-administered with mometasone furoate.

With respect to inflammatory cell infiltration into the dermis, the results in Table 10 indicate that the effects of a combination of auranofin (0.2%) and mometasone furoate is the result of synergism since the apparent IC_{50} is increased by about 3,800%. It is also possible that a lesser degree of synergism occurs with respect to the anti-

inflammatory action of betamethasone dipropionate in the presence of 0.2% auranofin. Here the increase in apparent IC_{50} is of the order of 400-500% (Table 10).

The results in Figure 2 show a massive synergism between mometasone furoate (5×10^{-6} M) and auranofin (0.2%). This combination produced an effect that was equal to that produced by 1×10^{-3} M mometasone in the absence of auranofin. Figure 2 also indicates that synergism may exist for the combination of auranofin with betamethasone dipropionate and fluocinolone acetonide, but not with hydrocortisone.

The results of these studies indicate that extensive synergism results from the combination of auranofin with certain corticosteroids, such as for example betamethasone dipropionate and fluocinolone acetonide as regards reduction of epidermal hyperplasia, and with others such as for example mometasone furoate as regards reduction of inflammation. Lesser degrees of synergism may exist between auranofin and other steroids.

Gold compounds and corticosteroids, as well as their formulations, which can be suitably used in the present invention have been discussed in detail in the present application or in Australian patent No. 616 755, which is incorporated herein by reference.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. A method of treating an immune-mediated disorder having one or more manifestations, comprising administering to a patient requiring such treatment a gold compound and at least one corticosteroid, wherein the at least one corticosteroid is selected to interact synergistically with the gold compound to exhibit preferential action towards one of the manifestations of said disorder or to exhibit equal action towards each manifestation of said disorder.

2 A method of treating an immune-mediated disorder according to claim 1 wherein the disorder has multiple manifestations.

3. A method of treating an immune-mediated disorder according to any one of the preceding claims wherein the gold compound and the at least one corticosteroid is administered simultaneously.

4. A method of treating an immune-mediated disorder according to any one of the preceding claims wherein the gold compound and the at least one corticosteroid is administered sequentially.

5. A method of treating an immune-mediated disorder according to claim 4 wherein the at least one corticosteroid is administered after the gold compound.

6. A method according to any one of the preceding claims, wherein the one or more manifestations of said disorder comprise an inflammatory component and/or a cellular hyperproliferation component.

7. A method of treating an immune mediated disorder according to claim 6 comprising administering at least two corticosteroids, at least one of which is selected to interact synergistically with the gold compound to exhibit preferential action towards the inflammatory component, and at least another is selected to interact synergistically with the gold compound to exhibit preferential action towards the cellular hyperproliferation component of said disorder.

8. A method according to any one of the preceding claims, wherein the disorder is an immune-mediated dermatological disorder.

9. A method according to claim 8, wherein the disorder is psoriasis.

10. A method according to claim 8, wherein the disorder is dermatitis.

11. A method according to any one of claims 1 to 7 wherein the disorder is rheumatoid arthritis.

12. A method according to any one of the preceding claims, wherein the gold compound is lipid soluble.

13. A method according to any one of the preceding claims, wherein the at least one corticosteroid is selected to interact synergistically with the gold compound to exhibit preferential activity towards cellular hyperproliferation in preference to inflammation.

14. A method according to claim 13, wherein the at least one corticosteroid is selected from the group consisting of betamethasone dipropionate and fluocinolone acetonide.

15. A method according to any one of the preceding claims, wherein the at least one corticosteroid is selected to interact synergistically with the gold compound to exhibit preferential activity towards inflammation in preference to cellular hyperproliferation.

16. A method according to claim 15, wherein the at least one corticosteroid is selected from the group consisting of mometasone furoate and betamethasone dipropionate.

17. A method according to claim 11 wherein the corticosteroid is selected from the group comprising hydrocortisone acetate, hydrocortisone, betamethasone, dexamethasone, fluocortolone 21-pivalate, triamcinolone acetonide, betamethasone valerate, alclometasone dipropionate, halcinonide, betamethasone dipropionate, mometasone furoate or fluocinolone acetonide.

18. A method according to claim 17 wherein the corticosteroid is selected from the group comprising hydrocortisone, betamethasone dipropionate, mometasone furoate or fluocinolone acetonide.

19. A method according to any one of the preceding claims wherein the gold compound is auranofin.

20 A method according to any one the preceding claims, wherein the gold compound is administered systemically.

21. A method according to any one of claims 1-19, wherein the gold compound is administered orally.

22. A method according to any one of claims 1-19, wherein the gold compound is administered locally.

23. A method according to any one of claims 1-19, wherein the gold compound is administered topically.

24. A method according to any one of claims 1-19, wherein the gold compound is administered by intra-articular injection.

25. A method according to any one of the preceding claims, wherein the at least one corticosteroid is administered systemically.

26. A method according to any one of claims 1-24, wherein the at least one corticosteroid is administered orally.

27. A method according to any one of claims 1-24, wherein the at least one corticosteroid is administered locally.

28. A method according to any one of claims 1-24, wherein the at least one corticosteroid is administered topically.

29. A method according to any one of claims 1-24, wherein the at least one corticosteroid is administered by intra-articular injection.

30. A pharmaceutical composition comprising a gold compound and one or more corticosteroids, the corticosteroid being selected to interact synergistically with the gold compound to exhibit a differential action towards a specific manifestation of an immune-mediated disorder, in combination with a pharmaceutically acceptable carrier, excipient, adjuvant or solvent.

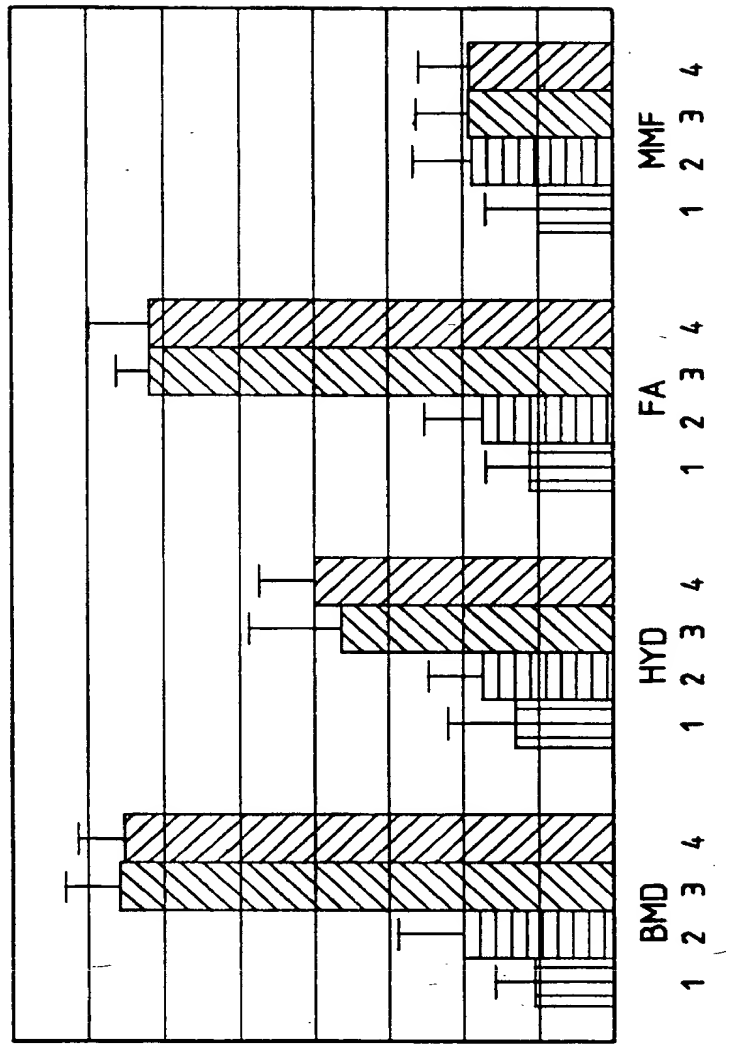
31. A pharmaceutical composition according to claim 30, wherein the composition is formulated for systemic administration.

32. A pharmaceutical composition according to claim 30, wherein the composition is formulated for oral administration.

33. A pharmaceutical composition according to claim 30, wherein the composition is formulated for local administration.

34. A pharmaceutical composition according to claim 30, wherein the composition is formulated for topical administration.

35. A pharmaceutical composition according to claim 30, wherein the composition is formulated for administration by intra-articular injection.



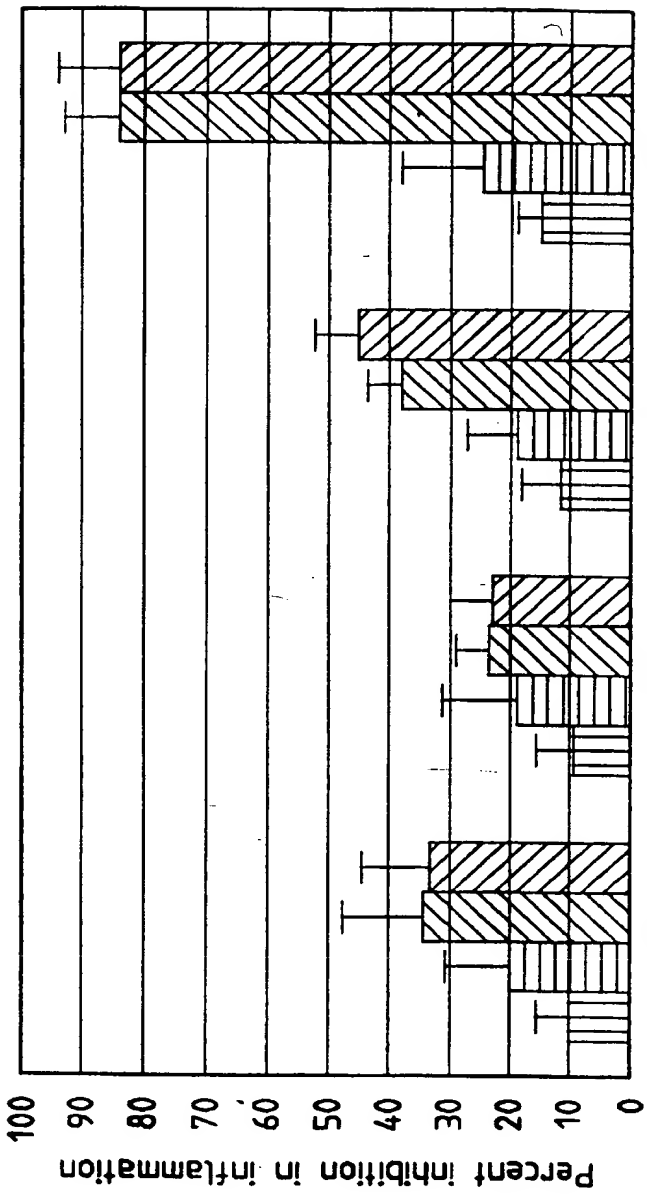
BMD
1. Auranofin 0.2%
2. BMD 1 x 10-5 M
3. BMD 1 x 10-5 M + AF 0.2%
4. BMD 5 x 10-4 M

HYD
1. Auranofin 0.2%
2. HYD 1 x 10-3 M
3. HYD 1 x 10-3 M + AF 0.2%
4. HYD 3 x 10-3 M

FA
1. Auranofin 0.2%
2. FA 5 x 10^{-6} M
3. FA 5 x 10^{-6} M + AF 0.2%
4. FA 4 x 10^{-5} M

MMF
1. Auranofin 0.2%
2. MMF 5 x 10^{-6} M
3. MMF 5 x 10^{-6} M + AF 0.2%
4. MMF 5 x 10^{-6} M

FIG. 1



BMD
1. Auranofin 0.2%
2. BMD 1 x 10-6 M
3. BMD 1 x 10-6 M + AF 0.2%
4. BMD 1 x 10-5 M

HYD
1. Auranofin 0.2%
2. HYD 5 x 10-4 M
3. HYD 5 x 10-4 M + AF 0.2%
4. HYD 8 x 10-4 M

FA
1. Auranofin 0.2%
2. FA 5 x 10-6 M
3. FA 5 x 10-6 M + AF 0.2%
4. FA 2 x 10-5 M

MMF
1. Auranofin 0.2%
2. MMF 5 x 10-6 M
3. MMF 5 x 10-6 M + AF 0.2%
4. MMF 1 x 10-3 M

FIG.2

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/AU 97/00747

A.	CLASSIFICATION OF SUBJECT MATTER
Int Cl[6]:	A61K 31/70, 31/28, 31/57, 31/58

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K 31/57, 31/58 and Keywords as below.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
AU: IPC as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Derwent: (Gold or auranofin or aurothiomalate or myocrisin or aurothioglucose or solganol) and (Glucocorticoid: or glucocorticosteroid: or corticosteroid: or mineralocorticoid: or betamethasone or fluocinolone or mometasone or hydrocortisone or fluocortolone or triamcinolone or alclometasone or halcinonide or dexamethasone)
Chemical Abstracts, Medline: As with Derwent above and (psoriasis or synerg: or demat: or immun: or rheumatoid arthritis)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	AU 34351/89 (616755) B (SMITHKLINE BEECHAM CORPORATION) 16 October 1989 Whole Document	1-35

[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 December 1997	13 JAN 1998
Name and mailing address of the ISA/AU AUSTRALIAN INDUSTRIAL PROPERTY ORGANISATION PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No.: (02) 6285 3929	Authorized officer **R.L. POOLEY** Telephone No.: (02) 6283 2242

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/AU 97/00747

C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	The Journal of Rheumatology, Volume 21, No. 3, issued March 1994 (Toronto, Canada), M. Heytman et al, "The Longterm Effect of Pulsed Corticosteroids on the Efficacy and Toxicity of Chrysotherapy in Rheumatoid Arthritis", pages 435-441 see especially page 438.	1-8, 11, 13, 15, 20-35
X	Journal of the American Veterinary Medical Association, Volume 186, No.1, Jan 1. 1995, U.S, 1hrke. P et al, "Pemphigus foloaceus in dogs: A review of 37 cases", pages 59-66 see especially page 65, 2nd column.	1-8, 13, 15, 20-35
X	Journal of the American Academy of Dermatology, Volume 16, No. 4, April 1987 US, Thomas .I et al, "Gold Therapy and its indications in dermatology", pages 845-854 see especially page 852.	1-8, 13, 15, 20-35
X	AU, 15456/88 (604542), B (ARTHROPHARM PTY. LIMITED) 10 October 1988 Whole Document	1-8, 10, 11, 13, 15, 17, 18, 20-35

INTERNATIONAL SEARCH REPORT
Information on patent family members

International Application No.
PCT/AU 97/00747

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
AU	34351/89	CA	1337928	DK	2270/90	EP	417105
		JP	7-025681	US	5527779	WO	89-09054
AU	15456/88	CA	1327354	DE	3854604	EP	356435
		JP	2-511829	US	5145841	WO	88-07060

END OF ANNEX